Human genetics. [Vol. 3], Memoranda received after January 31st 1995 / Science and Technology Committee.

HOUSE OF COMMONS SESSION 1994–95

SCIENCE AND TECHNOLOGY COMMITTEE

HUMAN GENETICS

VOL III

Memoranda received after January 31st 1995

Ordered by The House of Commons *to be printed*
6th July 1995

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LIST OF MEMORANDA

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Letter to the Clerk of the Committee from Dr Caroline Berry, Clinical Director, SE Regional Genetics Centre (HGC 115) (7 February 1995)

Re: SCIENCE AND TECHNOLOGY COMMITTEE INQUIRY INTO HUMAN GENETICS

I thought the following two cases, both involving adult polycystic kidney disease were relevant to your enquiry—particularly in relation to paragraph 3.5 of Human Genetics: Questions.[1]

Adult polycystic disease is a genetically determined condition passed from parent to child such that the child of an affected person has a 50 per cent chance of inheriting the gene. There is enormous variation in the degree of severity with which the gene manifests itself in different individuals. Those with cysts in the kidneys may develop high blood pressure and kidney failure over a period of many years. Renal transplant may be necessary in middle age but in many people this may not be needed till later in life, or even at all.

Case 1. A man of forty found to have polycystic kidneys after his child was found by chance to have cysts in the kidney. A recent intensive check up showed him to be entirely normal apart from the presence of the polycystic kidneys.

He works in the insurance industry and reports that he is now unable to increase his life insurance or mortgage. Should he wish to change his job he would be unable to do this as in a competitive situation his medical history would put him at a disadvantage to other candidates, despite his current good health.

Because of this he is declining to inform his brother and sister as he does not believe it is in their best interests to know whether or not they are affected. Each has a 50 per cent chance of having inherited the gene and if they have then the outlook for their kidney function would be improved by early diagnosis.

Case 2. A man of 36 was employed in a temporary capacity. This went well and there were plans to give him a permanent job. He had a medical examination at which he mentioned his polycystic kidneys and the offer of employment was withdrawn.

Thus people are being discriminated against and the matter needs to be addressed by both the insurance industry and employers in general and I hope your committee will be able to further this.

Memorandum from the Royal Society (HGC 116) (22 February 1995)

This response was compiled by a group under the Chairmanship of Professor P J Lachmann, Sec RS. The other members were: Reverend Professor G R Dunstan CBE, Professor J H Edwards FRS, Professor P A Jacobs FRS, Sir Aaron Klug FRS, Mr D Shapiro and Professor Sir David Weatherall FRS. It has been endorsed by the Council of the Royal Society.

Introduction

Humans are products both of their genes and their environment, and human disease is likewise due to both genetic and environmental causes. The genetic cause alone is sufficient in diseases such as muscular dystrophy, Huntington's disease and the thalassaemias: in other diseases the genetic cause plays an important role in making the subject more susceptible to environmental factors. This is now known to be the case in coronary heart disease and many forms of cancer. The striking advances in the understanding of human genetics that have come about in the last 40 years have already contributed substantially to understanding the genetic causes of disease and to the diagnosis of genetic abnormalities even before birth. Further genetic research will lead to the prevention of much genetically-caused disease as well as to its avoidance and treatment. Genetic research should be strongly encouraged for the beneficial results that will emerge.

The rapid advances in genetics and particularly the recently-discovered techniques of genetic intervention have given rise to some public concern. We believe this concern to be essentially misplaced. It derives, in large part, from the difficulty of keeping the public understanding of genetics abreast of the rate at which new knowledge is being acquired. It is hence particularly important to encourage genetic education, in schools. The principles of the subject can readily be taught on simple organisms such as the fruit fly *Drosophila*; the nematode worm, *Caenorhabditis elegans*, and the cress-like plant, *Arabidopsis*, all of which have played such important roles in genetic research. A proper understanding of these principles should dispel some of the fears that can arise from misconceptions about the purposes and methods of genetic intervention.

We therefore welcome this opportunity to respond to the Committee's questions.

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[1] For the list of questions posed by the committee see Human Genetics—Memoranda received up to January 31 1995—HC41-II, p. 1.

1. General ethical and regulatory

Genes carry the code which specifies the proteins that are made within a cell. Additionally, other regions of the genes carry the instructions that regulate the activity of these "structural" genes. Current genetic research aims to describe not only the structural genes, but also the regulatory genes that control them. The Human Genome Programme will increase our knowledge of both types of genes in man. Human genetics is also essentially concerned with the variation in the genes among different individuals. Studies of human genetic diversity are of the greatest importance in understanding predisposition to disease.

There is a well-established system in this country for looking in to the ethical aspects of all research on human subjects based on local ethics committees. In addition, funding bodies satisfy themselves on the ethics of projects which they fund. In the novel and publicly sensitive area of gene therapy there is also a central committee, the Gene Therapy Advisory Committee, which has substantial lay representation and which is required to approve all protocols in this area.

With regard to the ethical aspects of genetic screening programmes, we would draw you attention to the report "Genetic Screening: Ethical Issues" of the Nuffield Council on Bioethics whose conclusions and recommendations we generally support.

We firmly believe that the right to advance natural knowledge by scientific enquiry is fundamentally necessary and that for "society" to try to impose restrictions on the acquisition of knowledge would not only amount to a quite unacceptable form of intellectual censorship but also damage future prospects of human welfare. It is equally fundamental that all scientific research is carried out by methods that are ethically acceptable and that do not infringe the rights, dignity or welfare of the human subjects involved. Any application of the knowledge obtained for purposes that affect the public requires their informed consent. Geneticists are, in general, well aware of the wider social and ethical implications of their research. With regard to question 1.4, the information that has so far come from research into human genetics does not support a highly deterministic view of human behaviour. Impressions to the contrary given occasionally in the popular press emphasise the desirability of improving the general level of education in genetics.

The desire to improve the world is one of the driving motives of science and technology. Genetic intervention in food crops and livestock to improve yields and to increase resistance to infections has long been practised and is of proven value. In humans, the prospect of somatic cell genetic intervention to treat severe disease is to us ethically entirely proper. However, we do not believe that intervention in the human germ line (i.e., altering the characteristics inherited from one generation by the next) could be justified at the present time or in the foreseeable future. We would recommend to the Committee the Report on Gene Therapy presented to the UNESCO International Bioethics Committee in September 1994 which goes into this subject in detail, and whose conclusions we would in general endorse. We draw the attention of the Committee also to the Opinion of the Group of Advisers on the Ethical Implications of Biotechnology of the European Commission, Number 4, "The Ethical Implications of Gene Therapy", 13 December 1994.

You ask for advice on what should be addressed in the proposed UN declaration and treaty on the protection of the human genome. The paper by Knoppers and Chadwick "The Human Genome Project: under an International Ethical Microscope", Science, 265 (30 September 1994) 2035–2036, helpfully reviews "several areas of international consensus that could serve to harmonise eventual national regulation" according to five basic principles: "autonomy, privacy, justice, equity, and quality out of respect for human dignity". We also commend the Preliminary Outline of the Declaration on the Protection of the Human Genome prepared at the second session of the UNESCO International Bioethics Committee.

2. Public awareness and education

We believe that there is increasing public awareness of, and interest in, all aspects of genetics, particularly genetic engineering. Genetic engineering is sometimes presented to the public in a negative light as "unnatural dabbling in natural processes" or as "playing God". The basic processes of genetic engineering occur spontaneously in nature, in the transfer of genetic information among micro-organisms or from host to virus, and were *discovered* rather than *invented* by man.

As regards the benefits from genetic research there is likely to be a period of years between the acquisition of new knowledge and its application to the treatment of disease. The use of the new genetic technique of positional cloning as a tool for the diagnosis of genetic defects underlying disease has been brought into clinical use with commendable speed. In the introduction of all new modes of diagnosis and treatment a thorough evaluation of both risks and benefits has to be made. It is important that this is understood by the public. There is a danger that unreasonable public expectations for example that procedures must be free from any risk, may hinder the introduction of treatments which have substantial overall benefits. This problem has been encountered in the use of some vaccines.

While some diseases of genetic origin may result in quite dramatic changes of behaviour (for example Huntington's disease), there is every reason to believe that behaviour within a healthy population, like virtually

all other traits, is determined both by genetic and environmental factors. Furthermore, an understanding of the genetic component of behaviour allows the cultural and environmental contributions to be altered in a way that maximises an individual's potential.

3. Genetic disease

At present there is great interest in developing genetic diagnosis. As well as tests already carried out, there is much that is still confined to research programmes. It would appear that there are difficulties, often financial, in moving tests from research to routine practice. This is a problem in a health service that is short of funds and where it is difficult to persuade purchasers to contract for novel services.

You raise in 3.2 the question of ethical problems peculiar to somatic cell gene therapy. We believe that there are no ethical questions above and beyond those of standard medical treatments that need to be addressed in this context.

Maintaining the confidentiality of information about an individual's genome is very important, but the case is not fundamentally different from the use of other medical data. Medical information is normally made available to third parties only with the consent of the individual or when specifically required by law. Whether insurance companies or employers should be allowed to demand genetic tests for susceptibility to particular diseases is a difficult question. It is quite possible that where there is a genetic predisposition to an occupational hazard (for example, the risk of developing Goodpasture's Disease in subjects who are HLA [human leukocyte antigen] type DR2 and exposed to organic solvents) an employee who becomes sick as a result of this foreseeable risk may regard his employer as negligent in not having offered genetic testing. However, such HLA testing has been available for many years and does not appear to have been used significantly for employment or insurance purposes.

The NHS constituted as a universally available health system avoids the insurance problems of a system based on commercial or private health insurance which might wish to take account of genetic profiles before offering cover. Even so, informed interpretation of genetic profiles need not lead to loss of insurance cover. Genetic factors generally indicate only a predisposition to a disease rather than give absolute information that an individual will develop it. Such data are equivalent to information about family histories already used widely by insurance companies. Furthermore those who are aware of a genetic predisposition to disease are frequently able to reduce its effect by suitable life-style modification or medical treatment. The use of diet and drugs to treat those genetically predisposed to high blood cholesterol levels is a good example.

We consider the introduction of screening for genes causing or predisposing to disease should be restricted to those in which benefit to health may be expected (for example, in the case of phenylketonuria where a suitable diet can prevent the development of mental deficiency) and their introduction should not precede the availability of appropriate resources, including access to informed advice.

We do not foresee stigmatisation of people on account of their genetic profiles becoming a major problem. Every human being carries a number of genes for serious diseases that can be expressed in later generations if particular matings should occur. There are many examples of well known genetic "defects" in which the general public have shown little interest—such as the heterozygous carrier state for $\alpha 1$ antitrypsin deficiency and cystic fibrosis. The possibility of adverse public reaction to genetic screening would be lessened if the programme were accompanied by effective public education. A successful example of this approach is seen with sickle-cell disease; in several Mediterranean regions the resistance to malaria conferred by the sickle-cell trait is no longer an advantage in the modern, malaria-free environment. By educating the public to the past advantage in the heterozygote and the present danger of sickle-cell disease in the homozygote when both parents carry the trait, there is now no public hostility to widespread testing.

In some places termination of pregnancy has been made available if an unborn child who would develop sickle-cell anaemia is diagnosed. In other places, including those where abortion is opposed by the church (in Cyprus the Greek Orthodox Church and in Sardinia the Catholic Church) outstanding programmes of preconceptual screening have been established. The church authorities in Cyprus, for example, require that, before any marriage ceremony in church, the couple must produce certification that they have been screened for thalassaemia and appropriately counselled. The certificate does not, however, reveal the outcome of the test.

4. Economic benefits

The rational treatment of disease and the design of drugs may be greatly assisted by knowledge of disease mechanisms, of which particular genetic abnormalities associated with the diseases are an important part.

The factors mentioned in 4.3—technology transfer, patent protection and regulation—can all impede the commercial exploitation of research findings. The existing UK patent system is ill-equipped to deal with the new questions being posed by biological, and particularly genetic, material. The complexity of the issues is

magnified dramatically if one notes the differences in patent law and its interpretation between the European, US, Japanese and Chinese patent systems.

We know of no research that has failed to be funded because of the regulation of genetic-based research in the UK, but have heard of the relocation of laboratories from Germany where regulation is very restrictive. It is to be hoped that overly restrictive regulation will not be introduced here.

So far we have discussed human genetic research solely in terms of knowledge of, and impact upon, humans; but such research is just one part of a much larger spectrum of genetic studies on many different organisms using many different methodologies and technologies. Each area of activity feeds into the general pool of knowledge and each often benefits from activity in another. Great benefits will be derived from comparative genome research. The UK has a significant investment in this area, and non-human animal genome studies provide for the elucidation in this area, and non-human animal genome studies provide for the elucidation and experimental analysis of certain human diseases, (e.g., the recent convergence of work on malignant hypothermia in humans and porcine stress syndrome).

5. Research

The primary driving force for mapping and sequencing the human genome comes from scientists' desire to understand the complex phenomena that govern human development, structure and function in health and disease. What makes people what they are is a subject that has exercised the minds of individuals from all sectors of society, not only in the scientific community. Consequently, there is a general cultural interest in unravelling the "secrets of the genome".

With the development of sophisticated, rapid technology to sequence DNA, what had until recently been a distant prospect has now become a practical reality; and the mapping of the whole genome may be complete within a few years. Expressed genes, i.e., those that make a specific product, are being studied first, but it is apparent that many of the unexpressed regions also have important functions. A "physical map" of the complete genome provides a systematic approach. It also simplifies the task of identifying gene defects that initially have been mapped only to a rather broad region, and hence it facilitates the location, identification and regulation of the genes themselves.

In 5.3 you raise the question of genetic determinism which has already been touched on. Genetic background and environmental influences are inextricably interwined in producing variable characteristics; the advocacy of an exaggerated genetic determinism does no service to science or humanity. It offers false hope on the one hand and generates fear of the possible consequences of genetic manipulation on the other.

An enormous amount has been achieved in a short time in human genetic research with relatively modest investment in molecular genetics. A great deal remains to be understood not least in the area of mechanism. As mentioned earlier (see para. 1), the structural genes are not the whole story. Even when they are fully mapped there will still be complex interactions to unravel. There is a proper concern that gene-based therapies should be fully understood before they are brought into clinical use, to minimise the possibility of unforseen effects.

6. Evolution

Evolution occurring by genetic mechanisms takes place over periods measured in hundreds of generations. On average, a hundred human generations cover 2,500 to 3,000 years. Most of the "evolution" that has been observed in human society in historical times has been achieved by cultural and not by genetic mechanisms. Our progress is encoded not in our genome but in our spoken, written and pictorial records.

Furthermore, the great increase in the mobility of populations is giving rise to a human gene pool that mixes on an almost global scale. This has had the effect of introducing certain genes that had some advantageous effects in one environment (a good example is genes that cause changes in haemoglobin but afford some protection against malaria) into environments where these genes are only disadvantageous. Here human intervention, stemming from premarital screening and/or antenatal diagnosis, may accelerate the breeding out of particular harmful genes. In this way the burden of genetic disease can be reduced.

With other genetic disease (such as muscular dystrophy) the mutation rate is so high that such strategies can have only a limited effect. The idea that the efforts of human medicine or the social arrangements of a modern liberal democracy will lead to a deterioration of the quality of the human gene pool by mitigating the working of natural selection is not well founded scientifically, and has a most unfortunate political history. Moreover, there is wide agreement (see, for example the UNESCO declaration) that the use of genetic intervention for the purposes of "enhancing" human characteristics, as opposed to the prevention of significant human disease, is unjustified. As no genetic intervention in the human germ line is currently envisaged, it is only by traditional means such as choice of mate that we can deliberately influence the human gene pool. The only recent development that may produce a significant change in human populations within a few generations is the

introduction of prenatal sex determination, allowing parents to choose the gender of their offspring. In parts of the world where there is strong preference for male children, a widespread introduction of this practice could lead to significant imbalance between the sexes, a situation that would almost certainly have undesirable social effects.

Letter to the Clerk of the Committee from Alistair Kent, Director, Genetic Interest Group (HGC 117) (10.2.95)

Re: INSURANCE

It is our experience that some people experience considerable difficulty in securing insurance cover under present arrangements. Although we have no statistics on the extent of the problem, we do hear regularly from some of our member organisations about their members experiences. We held a conference on this theme about a year ago. A copy of the report is enclosed for your information.[1]

I have also been in contact with some of our member groups to ask them to let me have some examples of the sort of difficulties that their members have encountered and I will forward these on to you when I have them to hand.

It is difficult to generalise about the nature of the conditions that cause particular trouble, apart from the fact that they generally seem to be ones which are adult onset in nature, or which are particularly variable in their manifestation. Another group where difficulty is often encountered is people with conditions like cystic fibrosis, where treatment for those affected has improved such that those affected are now living into adulthood instead of dying before they ended childhood. For these people there is no real data to base insurance decisions on yet, so the treatment that they receive is variable to say the least.

Another problem occurs where conditions are found in a people from particular ethnic groups. As an example, because the UK population affected by Sickle Cell Disease is a fairly small one we understand that the actuarial data on which underwriting decisions are based derives from the USA, where access to health care is linked to income, and where black groups are to be found to a disproportionate extent in the lower income strata of society. As a consequence they tend to be less likely to receive treatment and so suffer from the effects of their condition more than may be the case in this country.

I would be happy to expand on the above points if this would be helpful, and will in any case write to you again when I have the examples currently being prepared by some of our groups.

Memorandum from Professor Brenda Almond, Social Values Research Centre, University of Hull (HGC 119) (10 February 1995)

1. General ethical and regulatory

1.3 The balance of ethical considerations in respect of the pursuit of scientific knowledge would seem very clearly to be weighted against prohibiting research areas on the grounds that they may lead to difficult moral problems. Most knowledge can be put to bad uses, and ethical problems really arise at the later stages where the findings are to be applied. (See below.)

1.4 Increased knowledge of genetics may lead to a deterministic view, but the sting may be drawn from determinism once it is recognised that each individual is unique; the threat people perceive in determinism is that of finding themselves to belong to a category of entities to which broad and inflexible causal laws apply. "Laws" which affect just one person are hardly laws at all. It is also useful to remember that an understanding of genetics is quite compatible with recognising that each individual, whatever their hereditary endowment, interacts with environmental influences. So determinism in a damaging sense is not applicable here.

1.5 Germ line intervention is a different case and certainly should be avoided both because of the unknowability (not merely "lack of actual knowledge") of the effects and because of impossibility of consent.

2. Public awareness and education

This is an important matter, and the point made in 1.4 above might well deserve to be better understood. More important, however, is to extend public awareness of the scientific facts and their social implications, if

[1] Not printed.

possible in order to reduce the possibility of social stigmatisation arising from from early identification of conditions. The promotion of health, by whatever means, need not generate intolerance of ill-health.

3. GENETIC DISEASE

3.4 Seeking information about prior conditions is very much advisable before conception of children, since this involves the well-being of both future partner and future children. But it should be recognised that there is more than one consideration here—the issue cannot be treated as a single issue, in particular it is important to distinguish:

(i) Serious conditions, particularly medical conditions which may be life-threatening or disabling, from trivial conditions. (The same conditions may also affect differentially different individuals).

(ii) The identification of 100 per cent probability that an individual will suffer from the complaint from a lower degree of probability, at bottom a minor statistical chance.

(iii) A disease and a predisposition to a disease (which may be affected or controlled by environmental factors).

(iv) Sex-linked complaints from those which affect both sexes equally, since it is possible to use sex selection to enable someone to have a healthy child, who might otherwise have decided not to risk having children at all.

(v) Late-onset diseases from early ones.

False positives and abortion

A serious problem worth singling out for attention is that of false positives. One must assume that screening will in fact lead to abortion in some cases. So the issue implicitly raises the ethical question of the justifiability of abortion. Even where that is accepted as morally justified under special circumstances, there is still a further problem: because of the false positives, for every affected foetus aborted, a number of healthy children will be lost. This is an important ethical issue in its own right.

Autonomy Informed Consent and Confidentiality

Implicit in these issues are some questions about the assumptions of counselling and investigating. The principle of autonomy which is commonly accepted as important in medical treatment entails a need to secure informed consent. But while it is usual to ask for consent to surgical procedures, people are seldom given the chance to give or refuse on an informed basis access to counselling and information. And in the case of the knowledge potentially available through genetic screening, information itself may have serious repercussions for the individual directly concerned and for relatives who have not been involved in the processes at all. Confidentiality, which is another ethical requirement associated with the principle of autonomy may conflict with the rights of some of those involved to share knowledge, once it becomes available to others. For example, I have heard of a case in which some relatives wished, posthumously, to discover whether a relative who died had suffered from Huntingdon's Chorea. They felt they had a right to this information in order to make their own reproductive choices. Other relatives, however, felt equally strongly that this investigation should not be carried out, since it would, they believed, adversely affect their own families, casting a shadow through the generations. It is difficult to see how such a disagreement could be resolved. The "harm" principle, often also referred to in medical ethics, also fails to resolve the matter since harm could result both from knowing and from not knowing the facts.

Letter to the Clerk of the Committee from Alistair Kent, Director, Genetic Interest Group (HGC 124) (28 February 1995)

Re: INSURANCE

Further to my letter of 10 February I have heard from a number of our members about problems that they have experienced, and I enclose copies of the information that we have been sent.[1] I have obliterated details where these would enable individuals to be recognised, but otherwise the information is as received.

Clearly the information is anecdotal, and we have no way of knowing how extensive the problem is, although it crops up in relation to a wide range of conditions and types of insurance cover. It is an issue that concerns many of our member groups. I suspect that many families may be put off seeking cover through fear of rejection

[1] Not printed.

or anxiety about being put into a position where they feel under pressure to acquire or to disclose information about themselves that they would rather not know or prefer to keep confidential.

Another issue that is difficult to quantify is the use that is made of "weighting" of premiums, and how decisions are arrived at. Again, I suspect that many just accept some additional loading without question.

The issue that concerns us is not so much the situation that exists now, based on past practice where assessment of genetic risk was imperfect. We are more worried about the impact of accurate DNA based tests with much improved diagnostic and predictive power and how this will be used by insurance companies. It is in this area that we feel regulation and control will be needed to establish a climate within which the availability of genetic information and the use to which it can be put is restricted. This is an issue where urgent movement to establish an appropriate framework is needed before custom and practice has allowed a framework which may be unsatisfactory to emerge.

I hope that members of the Committee will be able to give consideration to this issue, as it is one where rapid scientific advance will influence future possibilities in ways not immediately determinable from past practice.

Letter to the Clerk of the Committee from Russell Greig, Smithkline Beecham (HGC 126) (1 March 1995)

In response to your letter dated 23 February 1995, we are providing the following additional information as requested by the Committee:

WHAT IS THE PRECISE RELATIONSHIP BETWEEN SB AND HGS, HGS AND TIGR.

The following represents SB's summary of what we believe are the most pertinent aspects of these relationships considering your question. The full public text of the agreements and other associated information describing the relationships are enclosed for a more complete and accurate picture. Briefly:

HGS Agreement with TIGR.

In October 1992 HGS entered into a Research Services Agreement and an Intellectual Property Agreement with TIGR, a not-for-profit institute. Under the Research Services Agreement and the Intellectual Property, TIGR is obligated to disclose to HGS all significant developments relating to information or inventions discovered at TIGR, and HGS will own (on a royalty-free basis) all of TIGR's interest in inventions and patent rights arising out of TIGR's research during the term of the agreement (other than inventions and patent rights arising out of research that may in the future be funded by certain governmental and not-for-profit organisations). With respect to such rights arising out of research funded by governmental and not-for-profit organisations, under the Intellectual Property Agreement, HGS has been granted a royalty-bearing, worldwide, perpetual, exclusive license, except that the governmental or not-for-profit organisation may retain a non-exclusive royalty-free license.

HGS Agreements with SB.

Pursuant to the Collaboration Agreement, SB was granted a first right to develop and market products based on HGS's patents and technology for human genes and their expressed products in the "SB field." The "SB Field" is the field of human and animal healthcare, other than gene therapy (excluding gene therapy vaccines), antisense products and the use of genes for synthesising drugs that were known at the time the Collaboration Agreement was executed. SB has an exclusive worldwide license under HGS's patents and technology to make, use and sell products developed by SB.

Pursuant to the Collaboration Agreement, SB has (i) paid to HGS an aggregate of $63 million and with the stock purchase, an aggregate of $100 million overall to date. The Collaboration Agreement also provides for payments to HGS of royalties equal to a percentage of the net sales price of products made by SB within the SB Field ("SB Products") during any calender year. In addition, HGS will be entitled to product development milestone payments upon initiation of the first clinical study and upon acceptance of a New Drug Application or a Product License Application (or the equivalent) in a major market.

In addition to the payments under the Collaboration Agreement, SmithKline Beecham also purchased 1,012,673 shares of Series B preferred Stock and a warrant, exercisable under certain circumstances to prevent dilution, for an aggregate of $37 million in May 1993. SB agreed to purchase additional shares of Series B Preferred Stock for $25 million at such time as HGS has achieved Milestone III. Such payment will be reduced to $20 million if Milestone III is achieved after May 1996.

SB has been granted a first right to develop and market products within the SB Field that are based upon HGS's data, material know-how and inventions with respect to human genes ("Company Human Gene Technology") and are approved for development by a research committee during the initial research term (five years after disclosure of the number of genes meeting Milestone III). The research committee has equal representation by appointees of SB and HGS, with tie votes resolved either by senior management of SB and HGS or by binding arbitration. SB will be entitled to an exclusive license to use HGS's Human Gene Technology in SB Products developed pursuant to the Collaboration Agreement. If the Research Committee approves a research program, SB has 90 days after receipt of notice of approval to determine whether to undertake the research program. If SB elects to undertake a research program, but subsequently determines to terminate the research program or does not initiate the research program within six months of acceptance, it will be deemed to have rejected the research program.

HGS has retained the right to undertake a research program, and to develop and to grant sub-licenses with respect to products covered by an approved research program in the SB Field if SB elects not to undertake a research program approved by the research committee or subsequently terminates the program. If HGS develops such a product, the Collaboration Agreement provides that HGS will pay a royalty to SB with respect to such products on a comparable basis to the royalties payable to HGS on SB Products. If HGS licenses such a product to a third party, the agreement provides for the sharing of the license fees between HGS and SB. SB will also be entitled to royalties on P6 (i) products based on human genes outside the SB Field which are based on or incorporate patents or information developed by SB based on the HGS Human Gene Technology or pursuant to a research program or P6 (ii) products sold by HGS in the SB Field.

COPIES OF THE AGREEMENTS

Attached[1] are the following agreements of which the first four are publicly available through the United States Securities and Exchange Commission (SEC). Accordingly, some confidential business information has been redacted before filing with the SEC.

- The TIGR/HGS Research Services Agreement.
- The TIGR/HGS Intellectual Property Agreement.
- The HGS/SB Collaboration Agreement.
- The HGS/SB License Agreement.
- HCD TIGR database Form Agreements and HCD fact sheet.
- HGS Material Transfer Form Agreement.

By way of background, we are also providing you with the HGS Initial Public Offering Statement and the HGS first annual report. These documents[1] contain much useful information on HGS and their relationship with TIGR and SB.

WHAT ARE THE DIFFERENCES IN TERMS OF THE AGREEMENTS GOVERNING ACCESS TO THE HGS DATABASE VERSUS THE AGREEMENTS GOVERNING ACCESS TO THE TIGR DATABASE (HCD).

SB believes the principle difference in the two Agreements relates to what rights to inventions HGS has which are made through the use of the data provided by the two databases. In general:

(1) Access to the HGS database requires the Institution to grant HGS an upfront exclusive license at a preset royalty rate to such inventions; and.

(2) Access to HCD *Level 1* gives HGS/SB/TIGR no rights to any inventions that arise and access to *Level 2* requires the Institution to grant HGS an option to inventions that arise.

The HGS Material Transfer Agreement (MTA)

The standard MTA grants an up front exclusive license to Developed Technology to HGS. Developed Technology is defined to mean any and all data, formulas, information, compositions, biologics, substances and any intellectual property right thereto, including but not limited to, software, copyrights, patents and patent applications, which result from the Research conducted under the Agreement and/or use of the data and/or information provided by HGS. Further, the MTA provides for a preset royalty rate to be paid to the Institution on the net sale of Products sold by HGS and for a preset percentage of royalties received by HGS to be paid to Institution on the net sale of Products received by HGS from a sublicense.

The HCD Option Agreement

The HCD option agreement does not include an up front license. In its place, HGS, has an option to obtain an exclusive or non exclusive license to Inventions. Inventions are defined to mean any process, machine,

[1] Not printed.

manufacture, composition of matter, improvement or information conceived, discovered, reduced to practice or produced by any of Institution's employees, other staff members or students through the use of Data or Materials. Something is not an "Invention" and not subject to the option:

(i) If not conceived, discovered, reduced to practice or produced through the use of such Data or Materials, or

(ii) If conceived, discovered, reduced to practice, or produced through the use of like data or materials (prior to obtaining the Data or Materials from the Database) legally given by or obtained from a source other than the Database.

Within sixty (60) days following the disclosure of an Invention to HGS, HGS may exercise the Option in a license agreement to be negotiated within six (6) months. The license at a minimum will provide for the development of the Inventions into medical, diagnostic, therapeutic or other products.

Further, the HCD agreements empower the Institutions licensing office to make the decision whether or not a disclosure contains patentable subject matter.

Feel free to contact me should you have any further questions.

Letter to the Clerk of the Committee from Dr Mary Porteous, South East of Scotland Clinical Genetics Service (HGC 128) (9 March 1995)

Thank you for your letter of the 27 January. I am sorry to take so long to answer but I am having some difficulty in collecting together the information which you requested. I assume the costings request relates to the Presymptomatic Testing Programme which we run for individuals at risk of Huntington's Disease (HD).

Assume 25 Presymptomatic Test Requests per Year:

Minimum:

1 Consultant Geneticist Session 40 minutes.
1 Nurse Specialist Session 40 minutes.
1 Consultant Psychiatrist Session 40 minutes.

Laboratory time hard to cost as dependant on number of samples being tested at any one time. Higher throughput lowers costs significantly although the limited timespan acceptable in HD testing may lead to one sample being run alone.

1 Consultant result Session 40 minutes.

Follow up time is variable depending on result. Individuals with negative results tend to require only one follow up visit to the clinic although they are free to have as many as they feel they need.

Individuals given a positive result have very variable counselling requirements but probably average three further sessions of 40 minutes Consultant time.

Ideally each Consultant has 4 x 40 minute appointments in one half day session. One half day session is costed at £5,500 per year. An I grade Nurse specialist working on the same sessional pattern costs approximately £2,808 per year.

Working on these figures a crude cost per patient test and follow up would be:

6	Consultant sessions	£179.35
1	Nurse 40 minute session	£15.26
Total		£194.61

Assuming 25 tests a year (50 per cent positive) Total cost programme £4,865.20

Laboratory, Trust and Departmental administration costs would need to be added.

As I said in my presentation, I would expect testing for familial cancer to be based more on Genetic Counsellors rather than Consultant Geneticists although Consultants will have a supervisory role. This will keep costs lower. HD testing is a specialised area as, at present, no treatment is possible and involves small patient numbers so perhaps it is not the ideal model to base other testing on.

Figures relating to the total cost of Genetic Screening and Counselling will vary widely between Departments depending on population size and Department infrastructure. A report of a working group of the Clinical Genetics

Committee of the Royal College of Physicians: Purchasers Guidelines to Genetic Services in the NHS published by the College in 1991 might be helpful to you. Professor Brock could provide figures on the costs of population Cystic Fibrosis screening.

Memorandum from Professor Partha Majumder, Professor Anthropometry and Human Genetics Unit Indian Statistical Institute (HGC 129) (8 March 1995)

1. General ethical and regulatory

The ultimate goal of human genetics research is to rid society of the burden of all genetic diseases. Unfortunately, this ultimate goal may be impossible to attain because of complex interactions among genomic segments and of genotype-environment interactions. The present understanding of these interactions is far from being even superficial; complete understanding seems like a dream in the near future. Until the effect of genetic manipulations is understood without any ambiguity, germ-line manipulations can not be ethically permissible. Society does have the right to say "no" to such intervention strategies. However, I do not think that society has the right to regulate or prohibit the pursuit of knowledge; it only has the right to regulate the use of knowledge. Knowledge can potentially lead to problems, but history shows that lack of knowledge has resulted in more problems. Pursuit of knowledge should, therefore, never be regulated.

While I am against germ-line manipulation and do not believe that we shall amass sufficient knowledge to make germ-line manipulation a feasible proposition in the near future, I do believe that enough knowledge on function and regulation of genes and their effects will soon be gained to make somatic cell gene therapy a reality for many simple Mendelian diseases. Somatic cell gene therapy may not be unethical even with approximate and incomplete knowledge because only a single life is involved, provided that there is no other option for the patient and that appropriate and thoughtful consent is taken from not only the patient but also from all other individuals whose lives are tied to that of the patient.

2. Public awareness and education

In a country like India, there is very little public awareness of science. The average Indian's life is engulfed by unscientific thoughts and practices. Very little, virtually nothing, is being done to remedy the situation. The curse of illiteracy, which is mainly due to low economic standards, is all-pervasive in India. Even among those of us who have been fortunate to get education, many are scientists without the scientific temper. Science teachers in schools do not teach science, only scientific facts and some mechanical procedures used in science. A sea change is needed in India to impart scientific temper.

Among those who are interested in science, whether in the developed or in the developing countries, public awareness of genetics is low. "Genetic engineering" is a phrase that almost everybody knows, but very few are aware of the real meaning of this phrase. The accomplishments and methods of genetics are not clearly conveyed to the public. Current limitations of genetic are never conveyed. Both have led to anxiety and suspicion. Films like "Jurassic Park" have contributed to this growing, unjustified fear of genetics. Expectations of the benefits of genetical research are also unreasonable. In short, lack of proper information has resulted in a mystification of genetics. What needs to be done is the mandatory apportioning of every funded proposal in genetics for imparting public education in genetics. More special classes in schools, more articles in newspapers, more programmes on TV, are needed. The Government should subsidise genetics awareness programmes.

Regarding human behaviour, I think that much more research is necessary before one can even start addressing ethical and social issues that may emanate therefrom. Specifically, research on estimating genetic, environmental and genotype-environment interaction components to specific aspects of human behaviour need to be conducted. Such research should, of course, be preceded by unambiguous definitions of the specific aspects of human behaviour.

5. Research

Within the last decade, research in Human Genetics has progressed at an exponential rate and phenomenal advances have been made in the localisation of genes controlling many important disorders. The Human Genome Initiative has played a key role in providing the necessary thrust for this enormous acceleration of research activity. There have been many major technological and conceptual advances in the areas of molecular genetics, statistical and computing sciences which have been crucial to the generation, analysis and management of genetic data.

The ultimate goals of human genetics research are to understand

(i) The structure and function of all expressed genes.
(ii) The role of non-expressed genomic regions.
(iii) The nature of genotype-environment interactions in phenotypic expression; and
(iv) biology of the human individual.

To attain these goals it is essential to proceed in a stepwise fashion. There can be no question about the usefulness of gene mapping. Prediction of risk to a genetic disease is of unquestionable utility and in this context it is very important to map genes. The procedure of localisation of disease and other expressed genes is hastened by mapping non-expressed genes, and discovering that a disease is linked to a marker locus (which may or may not be expressed). Discovering such genetic linkage of diseases to marker loci greatly increases the precision of risk estimates to these diseases. Further, it speeds up the process of localisation of the disease/expressed genes. Sequencing of expressed genes is useful for discovering the nature and types of mutations that contribute to the various phenotypes associated with the locus in question. Sequencing of non-expressed regions around expressed loci is useful for understanding the nature of control exerted by these non-expressed regions over the expressed regions. Complete sequencing of the human genome will lead to an understanding of the nature of interactions within the genome, the similarities and dissimilarities among the control regions of expressed genes, and the like. Since this task of complete sequencing is impossible to accomplish in one go, many more years of preparation will be necessary. During these years of preparation, many more discoveries will be made and hopefully all expressed genes will have been mapped. Theoretically this task can be accomplished through piecemeal studies, but it is practically unlikely. One generally loses sight and track of the goal in the course of piecemeal studies.

Human geneticists have still a long way to go in estimating the relative roles played by genes and environment in the determination of human characteristics. While environment seems to play a neglible role in the determination of most simple Mendelian traits it is very likely that environment will be found to play significant roles in the determination of complex phenotypes. However, it must be mentioned that there is an increasing realisation that genetic factors are important even in so-called environmental diseases, such as infectious diseases. Further, my guess is that significant genotype-environment interactions will be detected for most complex phenotypes. I also guess that important epistatic interactions will be detected for such phenotypes. Human geneticists have just started scratching the surface of complex phenotypes; the road ahead is long and promises to be exciting.

It is difficult to quantify how much is understood about organisation of coding information in the genome, but all I can say is that we have learnt a lot, a lot is being learnt everyday, and a lot remains to be learnt. It is certainly conceivable that interventions such as those produced by gene therapy may have unforeseen effects, but if gene therapy is restricted to somatic cell gene therapy then the effects will be short-lived. However, in spite of the possible adverse effects, somatic cell gene therapy should not be abandoned because it holds a great promise in the treatment of genetic diseases and there may really be no adverse effects after all. However, gene therapy needs to be closely monitored both for positive and negative effects.

Memorandum from the National Council of Women of Great Britain (HGC 130) (1 March 1995)

1. GENERAL ETHICAL AND REGULATORY

1.1 *What do we need to know about the way genes work in order to make decisions about the use or regulation of genetic information? Are we likely to obtain that information?*

In our discussions on the opening question it became evident that a definition of "we" was necessary. It was agreed that there were broadly three categories:

(a) The general public where there is a worrying lack of understanding about the way in which heredity operates leading to anxiety.
(b) Those who would be involved in discussions leading to regulation. These would include lay members of the public who find themselves on ethical committees and indeed some professionals who may not have a true understanding of the implications and need counselling.
(c) People who have a strong antipathy to research in human genetics based not on knowledge but on "gut reaction", who find the whole topic morally and ethically unacceptable. Where this view is held it is usually very strong.

At the moment there is little confidence that information will be readily available without Government support.

1.2 *Are the current policies being pursued by the MRC and other research funding bodies with regard to ethical and social consequences of research in human genetics adequate?*

Although we have confidence in the probity of the MRC and other research bodies there is some concern that enthusiasm and drive towards a goal might result in a "blinkered approach". In the 1994 NCW Conference

Resolution (submitted to you in November), we asked the Government to set up an independent body to monitor the whole field of genetic research with particular reference to long term effects. We note with interest the comment in the report of the UK National Consensus Conference on Plant Biotechnology (November 1994, p. 15); "we suggest that a Government Minister should oversee this vast new development so that opportunities to benefit humanity are not lost in the face of the challenges it offers". This was strongly reflected in the views of our members.

1.3 *Has Society a right to declare that some research topics should be prohibited because they are intrinsically likely to lead to insuperable moral problems? Should geneticists think more widely than their immediate research goals and their likely consequences or should they leave that to others? Are they pursuing hidden agendas of which the public is unaware?*

NCW membership is drawn from a wide spectrum as shown by the broad range of work carried out by its Special Committees. These draw on professional expertise as well as on the views of non-specialists. Overwhelmingly the response showed that research must continue, but as moral problems cannot always be foreseen then the need for stringent regulation and monitoring of the use of the results of the research is vital. There is already a fear that the work with plants and animals is proceeding faster than legal regulations can be put in place. If this presents a problem how can we be reassured in the field of human research? As the public cannot be aware of the "hidden agendas", the geneticists should be accountable to non-specialists and be aware that their work could have implications for all, morally, ethically and socially.

1.4 *Does research into human genetics lead to a deterministic or any other particular view of human behaviour? Will people try to improve the world through genetic intervention? Should they?*

As human behaviour is multi-factorial, there will be an interplay of environment and inheritance. At the present the extent of knowledge does not allow for a deterministic or any other particular view of human behaviour. However, much research is being carried out into criminal behaviour with unforeseeable results, which could change attitudes. Wholesale population genetic interventions should not be encouraged even if they were practicable. Our generation is only too aware of what can happen. However, within small groups on medical grounds, it is acceptable to attempt to eliminate serious diseases, e.g., thalassemias, with the proviso that the individual's rights are paramount.

1.5 *Germ line intervention would affect later generations who cannot give their assent. Are there other objections in principle to it which go beyond our limited knowledge of what those effects might be? Would this be playing God? What does this mean, and why would it be wrong?*

Although there is a widespread reaction against germ-line intervention affecting future generations, further discussion often changes attitudes. Reflection indicates that much medical progress would have been halted if such views had been held in the past. This proved to be a very difficult question as generalisations cannot be made. The views ranged from objections in principle, often based on strongly held religious conviction to powerful maternal instincts to protect the unborn child from inherited handicap. The present generation must have the right to make its own decisions.

1.6 *What should the proposed UN declaration and treaty on the protection of the human genome say?*

Comments on the protection of the human genome were:

(a) Research must continue as the mapping of the whole genome may reveal important functions not yet foreseen.

(b) Co-operation between UN countries is welcomed but as developing countries take up their research programmes the treaty should provide for a sharing of knowledge as well as the rigorous controls.

(c) Concern was expressed about differing attitudes to patenting in, for example, the USA and UK. Knowledge should not be patented. Discovery of applications based on the knowledge with a declared utility could be acceptable for patent. This would give protection for the human genome.

2. PUBLIC AWARENESS AND EDUCATION

2.1 *What is the extent of knowledge of and interest in genetics among different sectors of the public. Should steps be made to improve this and, if so, what form should they take?*

2.2 *Is there a general anxiety and suspicion about research in genetics? Is it justified or should it be allayed and, if so, how?*

Unfortunately there is a general anti-science attitude among some people, particularly women, whose experience of science at school has left them feeling inadequate when asked to comment on scientific matters.

There have been steps taken in NCW to address this through the work of its Science and Technology Committee and a full day open to the public (8 March 1994) to celebrate "Creative Technology". Through the work of our Committees we regularly respond to consultative papers issued by Government Departments.

In our view many people are apparently untouched by these issues, until confronted by a specific question, when anxiety and suspicion develop, often based on ignorance and misinformation. A programme of education targeted as specific groups would improve the situation.

(a) Children: we appreciate that genetics is included in the new proposals for science in the National Curriculum. We hope that this will include not only the facts but the implications for society.

(b) The general adult population: we would recommend:

(i) More consensus conferences to involve lay people, such as recently held on Plant Biotechnology and quoted in the BBSRC January issue as "worth every penny".

(ii) Study days similar to those held by organisations such as NCW.

(iii) The use of existing networks, e.g., NCW, Soroptimist International, Rotary clubs, churches etc. to stimulate debate, perhaps based on study packs issued by the Government.

(iv) Pre-conceptual counselling should be freely available through Family Planning and other clinics, particularly for those families with a history of genetic disease.

(v) The use of the media in a responsible way, not the sensationalism of some outlets, could be a powerful tool in education. Why not include a genetically affected family in a soap opera? A recent article by Nigel Hawkes in "Woman and Home" must have reached many houses, and this is to be encouraged.

2.3 *Are there unreasonable expectations of the benefits that might come from genetics? If so should these be tempered?*

The media often report new scientific discoveries with implications of potential benefits. The time taken for development of new medical therapies is often far longer than indicated. This causes unreasonable expectations. Premature reporting of medical developments can give rise to disappointment.

2.4 *Is there a danger that genetics will be seen as an excuse for socially unacceptable behaviour? Could it be used to justify reductions in social programmes of health, education and welfare?*

As stated in 1.4 human behaviour is multifactorial. It is necessary to guard against apportioning blame for socially unacceptable behaviour to genetics; reduced social programmes cannot therefore be justified. As we cannot quantify the balance between nature and nurture there is an argument for enhanced support programmes to deal with genetically disabled individuals.

2.5 *What are the right questions on the bearing of genetics on human behaviour, ethics and belief?*

The consensus was that everyone would have a different set of questions according to their own ethics and belief. However, the right of individuals to choose their own standards of behaviour within a cultural and legal framework must be safeguarded.

3. Genetic disease

3.1 *How much of genetic diagnosis is conducted as a routine medical service and how much is associated with research programmes? Is the continuity between the two sufficiently well organised? Are some diseases with a known genetic cause not being diagnosed and, if so, why not?*

We have no figures on which to base answers to the first two parts of this question. In our view there are some genetic diseases not being diagnosed in patients for a variety of reasons:

(a) Lack of skilled recognition of early symptoms.

(b) Reluctance to be screened.

(c) Cost.

(d) An added factor is that although increasing use of genetic screening may demonstrate that everybody carries some genetic disability, e.g., recent work on Alzheimer's disease shows that one in 30 people may carry a protein mutation linked to the dementia condition, knowledge of this could cause undue suffering especially as there is no cure for the disease to date.

3.2 *Are there any ethical questions about somatic cell gene therapy which are different from other types of therapy which affect only the patient receiving them?*

The consensus was that no different ethical questions were raised as only one individual was involved.

3.3 *Should information about an individual's genome be regarded as confidential or should it be possible for employers, insurance companies etc., to require genetic tests or to obtain the results of previous tests on an individual or their relatives? If not, why is genetic testing any different from current medical tests?*

3.5 *If screening for a wide range of genetic predispositions becomes routine, how will people be protected from discrimination on the grounds of their genotype? Should they be?*

Information about an individual's genome should be absolutely confidential to ensure that no-one with a vested interest, e.g., insurer and employer, could discriminate. Too much information on a person's medical condition is already available. The following points have been considered:

(a) If screening is to remain voluntary then confidentiality is vital to maintain a fair field.

(b) The clause in many insurance policies whereby the withholding of information makes the policy invalid needs review.

(c) Even if a gene defect is present the disease may never develop so the person would not be a greater insurance risk.

(d) There is an assumption that all tests are accurate and this is by no means true.

(e) The insurance companies have so far relied on mortality graphs. Why cannot this technique be continued?

(f) Does everyone need life insurance?

(g) Should screening ever become routine?

3.4 *When is population screening for genetic disease appropriate? What factors, such as cost and the availability of counselling and treatment, should be taken into account? How should screening be organised and regulated?*

We cannot foresee a situation in which population screening could be practicable or desirable.

3.6 *Would people be well advised to seek genetic information from sexual partners before the conception of children? Are they likely to? Is this likely to change with future research?*

When there is a family history of genetic disease, pre-conceptual screening and counselling should be available to those who seek it. Genetic knowledge has implications for whole families some members of which may prefer to remain ignorant of the fact, especially where there is no treatment available. Future research may not change attitudes.

4. Economic benefits

4.1 *What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?*

4.2 *Are there differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?*

4.3 *To what extent do factors, such as technology-transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?*

4.4 *How does the regulatory regime for genetic based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential?*

We do not have access to the information on which to base opinions on this section. The following comments may be of interest:

(a) As stated earlier, if gene therapy is directed at somatic cells only, then we see no differences between this and conventional treatment.

(b) Commercial pressures to patent all the outcome from work on a particular gene could inhibit research in other laboratories and have consequences for the economies of some countries, especially in the third world, e.g., pyrethrum.

(c) Competition between multi-national companies can lead to strange situations, e.g., Flava-Sava tomatoes.

(d) There is a danger that the benefits from research funded by the tax-payer in the UK, are reaped elsewhere through lack of financial support to carry the technology through to the market place.

(e) Although we feel that there is room for improvement in the regulatory regime in the UK it compares very favourably with that of other countries who export their products to us!

4.5 *What products, other than medical diagnostics and therapies, might be produced as a result of human genetic research?*

The possibilities are endless. For example, through new techniques the transfer of human genes to plants and animals is already a reality.

5. Research

5.1 *Why is it worthwhile to map and sequence the human genome? What are the relative advantages of mapping expressed genes only versus completely sequencing the genome?*

5.2 *What will it tell us about the human species and the individual that would not otherwise accrue from piecemeal studies?*

5.3 *To what extent are human characteristics determined by the genome and to what extent does the environment influence the expression of genes?*

5.4 *How much is understood about the organisation of coding information in the genome? Is it conceivable that interventions such as those produced by gene therapy might have unforeseen effects?*

5.5 *Is the financial support for research in human genetics adequate when compared with the results which may flow from it?*

Most of these questions have been covered in earlier sections. However, we make the following additions:

(a) There is real concern that manipulation of one part of the DNA molecule by using recombinant techniques may have unforeseen effects on the whole organism itself and on future generations.

(b) In spite of our acceptance of somatic gene therapy there is a question over any possible link to germ line therapy not yet envisaged.

(c) The search for knowledge will always continue but be costly. The results that flow from it are not always in direct proportion to the money spent on it. Prioritisation is essential.

6. Evolution

6.1 *What evidence is there of continuing evolutionary change in humans?*

We have no statistical evidence on continuing evolution, but where the theory of evolution was accepted by our members it was thought to be continuing. For example, change in jaw size and reduction in number of teeth.

6.2 *What may be the consequences of modern social organisation for human evolution?*

The ease of transport today has led to less isolation and therefore interbreeding; and a consequent wider mix within the gene pool.

6.3 *What may the consequences of environmental change be for human evolution?*

Man has become adept at controlling his immediate environment (e.g., cental heating), but the total of increasing population and consequent environmental pressures on the finite resources of this planet must have implications, e.g., drought in parts of Africa could cause the loss of a whole tribe.

6.4 *What may be the consequences of the pursuit of scientific knowledge for human evolution?*

In nature the driving force for evolution has been explained by Darwin's "Survival of the Fittest" theory. The application of scientific knowledge has largely removed that factor from human evolution.

6.5 *What might be the evolutionary impact of selective fertilisation or termination and of other forms of extreme discrimination?*

If carried out on a large scale as proposed in China and attempted in other regimes, the prospect is frightening.

6.6 *In what way does manipulation of the germ line in the clinic or laboratory differ from natural variation?*

Natural variation takes place more slowly and is random, producing both "good" and "bad" genetic changes. One assumes that manipulation in clinic or laboratory is aimed at the elimination of "bad" genes.

6.7 *Human evolution has been by sexual reproduction guided by human behavioural drives. Should clinical interventions be allowed to interfere with this process?*

Clinical interventions is acceptable only in:

(a) The treatment of infertility.

(b) To avoid hereditary diseases.

Social reasons for clinical intervention were unacceptable to the members who responded to this questionnaire.

Memorandum from Merck, Sharpe and Dohme Limited (HGC 131) (3 February 1995)

Q1. *What assistance in the treatment of disease or the design of drugs is given by knowledge of the gene(s) associated with a particular disease?*

A1. It is worth pointing out that the majority of human disease is not linked to abnormalities of a single gene. Where this is the case (i.e., cystic fibrosis) such knowledge is of huge potential importance in furthering understanding of the disease and suggesting rational approaches to therapy, whether these are conventional or gene based.

Many other diseases are associated with genetic risk factors, the understanding of which is harder to quantify in terms of direct application to drug design, but whose identification will in any case enhance basic knowledge of the disease process and provide a stimulus for further research. It is simplistic though, to assume that even a complete understanding of the genes associated with a particular disease will have an immediate impact on therapy.

Q2. *Are there any differences, in principle or in practice, between gene and conventional therapy? How might these affect development costs? How will this affect the actual cost of treatment?*

A2. There are fundamental differences in principle and practice between gene and conventional therapy. Conventional therapy, with some exceptions, tends to treat the symptoms of a disease (I do not include antibacterial, antiviral and antineoplastic agents obviously), while gene therapy should be directed to the root cause.

If the disease is monofactorial then gene therapy should have a very high probability of success assuming that the problem of delivery of genes to the target tissues can be overcome. Failure to demonstrate efficacy should be much less of a problem than with conventional drugs. The entire process of development is therefore different.

For genetic therapy, design of the drug is self evident once the faulty gene has been identified. If effective methods for expression of the gene in patient tissues are established, then a single or infrequent treatment should be sufficient, thereby reducing the incidence of both mechanism and nonmechanism-based side effects drastically. The development process could be different, i.e. different types of pharmaco-kinetics studies which may or may not lead to reductions in time and cost.

As mentioned earlier, it is possible that only a minor proportion of human disease may be amenable to gene therapy, and secondly, there remain fundamental problems with delivery of such treatments to the patient.

Q3. *To what extent do factors, such as technology-transfer facilities, patent protection and regulation, influence the commercial exploitation of research findings?*

A3. It is believed that widespread application of the new knowledge of the human genome to medical research will lead to new, improved therapies for existing diseases and to therapies for diseases for which there have been no methods of treatment. New and improved therapies can only come about if researchers, academic and industrial, have rapid access to the genetic knowledge as it is generated.

The risk involved in commercial development and marketing of therapeutic agents is generally offset by an exclusive patent position. Genetic information, a gene or an encoded protein, can be patented as a therapeutic product for a specific disease, or, much more commonly as a tool for further research and drug discovery. If a patent which covers a product and a research use is licensed exclusively, researchers may not have access to the licensed subject matter for research purposes and further research could be impeded.

Merck has taken a position that while a product could be licensed exclusively, rights for research purposes should be licensed non-exclusively. It is envisioned that the non-exclusive license for research purpose only would be available for a reasonable fee.

The Merck Gene Index is an example of a pharmaceutical company working together with academia and government to generate human genomic information which may be accessed by anyone. The project will report sequence information directly to public databases and allow all interested parties unrestricted access to the Merck standard libraries of cDNA clones. Merck believes this approach will help ensure the advancement of science in the field of human genome research and biomedical sciences and will improve the overall chances of discovery of human therapeutics.

Q4 and Q6 *How does the regulatory regime for genetic-based industry in the UK compare with that in other countries? Is there a danger that investment will be lost to other countries with different regulations or with better venture capital funding potential? Is the UK a good place to conduct such research?*

A4 and A6 There is no doubt that the US has been quicker off the mark to recognise the validity of gene patents while Europe, including the UK, has been making up its mind. While this may have been a factor in the more rapid development of a gene industry in the US, the readier access to venture capital is a more likely explanation.

The regulatory attitude to genetic therapy is not hostile in the UK and we are probably as well placed as any country to carry out this kind of work. The role of the small venture capital-funded biotech companies should not be overemphasised. Most will need to sell their IPR to a major company or go into partnership at some stage and the present state of expertise of the UK pharmaceutical industry puts it in a good position to take advantage of this.

It must be pointed out, however, that the UK is unique in using a profit-regulation mechanism, the PPRS, to control drug costs. As we have emphasised on a number of occasions, this acts as a clear disincentive to research and tends to drive away foreign investment. Any draconian demand-side controls, such as generic substitution, will affect pharmaceutical companies ability to make a fair return in the UK, and thus will have the same effect.

It should not be supposed that the major companies are idly standing by while the genetic information revolution takes place around them. The majors are involved themselves and ultimately are likely to become the principal producers of novel gene therapies.

Q5. *What is the involvement of your company in genetic research? Have you any products currently in development based on such research? Approximately what proportion of products under development does this represent? Do you expect to develop such products in the future? If so, will you do so in house, through collaboration with academics or through acquiring IPR? Do you expect to carry out such activities in Europe, North America or elsewhere? Please indicate if any of your answers to this question is to be treated as commercial in confidence.*

A5. Merck's current emphasis is on conventional, (i.e., small organic molecule) drugs rather than on gene therapies. However, the majority of our present development candidates are based on knowledge of the gene to whose product the drug is targeted. In the future, there is no doubt that all our programmes aimed at discovering drugs that have effects on human biology (as opposed to microbiology) will have used the target gene product as part of the discovery process. The necessary genetic information is either obtained in house, or through academic collaboration or quite commonly, by in-licensing from academic and industrial laboratories, principally in the US and Europe. Access to such information is as vital for the present development of novel conventional drugs as it is for future gene therapies.

Memorandum from British Technology Group Ltd (HGC 134) (21 March 1995)

Whenever the patenting of human genes is discussed in lay circles, there is a danger that different issues can become muddled. Four of the most important issues are as follows:

(1) The morality issue.

(2) The issue of whether something pre-existent in the natural state can be patentable.

(3) The issue of whether it should be permissible to patent something which has no definite use, as in the products of human genome sequencing research.

(4) The issue of whether the grant of patents for human genes could block off whole areas of research and development, to the detriment of scientific knowledge.

All these four issues are facets of much wider policy or legal considerations. None is special to human genes. Taking them in turn:

(1) There are many questions involving consideration of morality on which there is no clear consensus. Simple examples are abortion and euthanasia. If and when a clear consensus emerges that the sale of parts of the human body is morally wrong—and that will include blood and proteins necessary to sustain vital functions in patients who cannot make the proteins themselves—presumably governments will agree that such contracts for sale are unenforceable. There is a precedent for this in the UK in Section 18 of the Gaming Act, 1845, which makes betting contracts unenforceable. Of course, this has not prevented betting and no law about sale of parts of the human body is likely to prevent their sale. Nevertheless, the enactment of such a law would be an important first step to take, if it appears that there is a moral consensus against such sales.

So long as there is no moral consensus and no law which has the effect of making certain contracts unenforceable, there can be no legal problem in an individual selling his genes (or cells) to third parties. Given that there is a patent system, he should have the right to apply for a patent to prevent someone from copying his genes—remember that the product sold can easily be multiplied to make thousands of copies quickly—and selling them. Otherwise, others may commercialise those genes. (Of course, if the genes have already been isolated by someone else or if it is obvious that they are desirable and could be isolated, then he would not get a patent, but that is an entirely separate issue). That X is free to sell his genes, X is debarred by law from patent protection and Y can then sell X's genes would be an absurdly unfair result.

(2) There is nothing new in the granting of patents for substances isolated from nature. For scores of years, chemicals have been obtained from the leaves of plants, proteins from animals, micro-organisms from the soil. Bacteria come from nowhere sometimes. In one BTG invention a bacterium which makes a heat-resistant enzyme had simply landed on the inventor's culture plate, perhaps having been blown in through the window. All these substances have been patented as isolated products. DNA is a chemical molecule and as such is no different in principle from any other chemical molecule, for example a rubber or a perfume molecule.

The basis of patenting substances extracted from nature is that it has required technical skill to find them or extract them or both. Such substances are only patentable if there is a degree of unpredictability or surprise in finding them or extracting them. Patent protection in these circumstances is necessary. Companies are not going to spend money investigating (say) the genes which make nerve proteins if their investment will not be protected by a patent monopoly.

(3) No one in patent circles wishes to defend the patentability of a substance which has no proper use. If the DNA does not have a proper use, it cannot validly be claimed in a patent. It is a question of defining what is a "proper" use. For example, practically every solid, water-insoluble substance will kill weeds if placed on top of the weeds in a thick enough layer or can be used to fill a sock to make a draught-excluder. What separates such silly uses from proper ones is that a proper use must be one which does not depend on a known property of substances of the same type. Consider, for example, a short DNA sequence isolated from human chromosome 18 and defined by its sequence. DNA is a double-stranded helix, but when heated it unwinds and becomes two separate strands. Take one of these single strands and tag it by substituting some radioactive atoms for normal atoms. This tagged DNA can be used as a probe which will "home in" on the part of human chromosome 18 which contains the sequence of its other strand. Thus, the single radioactive strand of the isolated sequence probe DNA will bind to a single strand of a sample of DNA from human chromosome 18. When this binding occurs, the latter becomes radioactive because it has bound to the radioactive probe. None of this is any surprise. To state in patent specification *merely* that this isolated DNA sequence is useful as a diagnostic probe for human chromosome 18 therefore is not a proper use. It is merely reciting a known property of DNA, just like reciting the known property of a solid substance above. What would be a proper use is to say that it is a diagnostic for a sequence on human chromosome 18 responsible for Smith's disease. That is attributing an important medical property to the isolated sequence and is *not merely* reciting a known property of DNA. "Some awareness of function" (MRC evidence, 23 November 1994) is not enough. There must be a definite use.

(4) Throughout industrial development there have been concerns that monopolies will prevent a particular industry from becoming developed. Somehow, these concerns have never materialised as facts. One should certainly be aware of defining areas of industry in which patents are not permitted, as the next area, almost by definition, cannot be foreseen. It could only lead to anomalies, e.g., a drug being marketed because investment in the drug can be protected by a patent, while the arguably superior gene therapy cannot.

It is no different from saying in the 1930s that certain valves should not have been patentable or in the 1950s that transistors should not have been.

One topic which has attracted much comment is the "polymerase chain reaction", which is a way of multiplying DNA in the laboratory without having first to put it into bacteria. Many scientists object to having to pay a royalty to use the process. Yet, there is nothing new in a company having an area of rich reward for an invention. Most diagnostic testing for proteins and antibodies uses a technique called "ELISA" (enzyme-linked immunosorbent assay). It was invented in about 1972 and the subject of patents by a Dutch company. BTG has profited from patenting cephalosporin antibiotics. There are and were alternative technologies for use in all these examples.

Another complaint is that if a company has a patent on (say) hepatitis C genes, no one else can do research in that area. *This is incorrect*: experimental (research) use of a patented process is not infringement. What normally happens is that such research results in an improvement, which can also be patented. The first company in the field will need the improvement, while the second company needs to be able to operate under the main (first) patent. The two normally come to terms by cross-licensing each other under the main and improvement patents. The system has worked very well, not least in the United States which has a flourishing biotechnology industry.

Finally, we would like to observe that it could be misleading to say that intact human genes are not patented. Certainly, there are many patents for long human DNA molecules (so-called cDNA) which behave like intact genes, (because they contain all those parts of genes which are responsible for making proteins). BTG has patent rights on DNA coding for the blood-clotting substance, factor IX, which it has licensed. The umbrella of patent protection is affording companies the opportunity to make factor IX from the DNA, thereby to treat haemophilia more safely.

Also parts of human genes—and not necessarily those parts which produce the amino acids for proteins—are patented. The human genetic make-up contains various "tools" which can be used more widely than for the particular genes with which they are associated. They regulate the way in which DNA makes proteins. BTG has a patent application for one of these sequences.

Memorandum from Dr Pushpa Bhargava, Anreshna Consultancy Services (HGC 136) (15 March 1994)

REPLY TO THE QUESTIONNAIRE[1]

1.1 We should decide on the use or regulation of genetic information on the basis of what we know at the time, with flexibility built in for changes in real time as our knowledge increases.

1.2 I don't know fully what these policies are as of today.

1.3 No, but the society has the right and the obligation to decide how the results of the research would be used or not used. No scientific discovery has ever led to insuperable moral problems nor is it likely to happen in the future. All scientific research must be transparent.

1.4 First question: No.

Second and third questions: They surely would and should, for example, by curing inherited diseases. Any attempt that is immoral or unethical must, of course, be regulated.

1.5 I do not see any such objections. Taking care of a genetic disorder through germ-line intervention is not playing God—not any more than a heart or corneal transplant is!

1.6 That all knowledge acquired on the human genome anywhere would be in the world public domain.

2.1 Very little around the world in both developing and developed countries. One way of rectifying this would be interesting TV programmes and books, and continuing education programmes at institutions of higher learning.

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[1] See Human Genetics—Memoranda received up to January 31 1995—HC41-II, p. 1.

2.2 I believe it is so in some countries. It is justified and is due to ignorance which should be tackled as mentioned in 2.1.

2.3 Yes.

2.4 First question: Yes, but it may be a reason and not an excuse (e.g., if there is a gene determining homosexuality or compulsive gambling).

Second question: I do not see how it could be used to justify such reduction.

2.5 Human behaviour and concept of ethics are surely (at least partly) determined by genetics. It would be exciting to know how. Beliefs are probably largely cultivated, though tendency towards certain beliefs might be inherited.

3.1 I cannot answer this for Britain.

3.2 No. At least I don't perceive any such questions.

3.3 Genetic testing should not be considered any different from other types of medical testing.

3.4 First question: Only for research purposes and epidemiology, for which names are not required, or when a group demands it.

Second question: For research and epidemiology, the Government or other sponsoring agency should pay. For individuals or groups demanding it, the people concerned should pay.

Third question: By careful evaluation of the objectives.

3.5 Discrimination should not be allowed but making a distinction between individuals for a particular job, based on genetic screening would be perfectly fair. (Why are the chosen basketball players taller than the average? Would this be called "discrimination"!)

3.6 Yes. And they would increasingly want to do so.

4.1 A great deal, for knowledge of the gene allows one to understand the mechanism of a disease, which understanding is bound to help treatment eventually.

4.2 There are differences both in principle, and in practice. There is no conventional therapy available (or even possible) for genetic disorders.

4.3 To a great extent. Hybridoma technology would have, for example, never developed to the extent it has, had Cesar Milstein patented it.

4.4 First question: I do not know.

Second question: It is always possible if the regulatory regime is not realistic.

4.5 Other products are most likely to be produced, though one cannot say precisely which ones. Agents that would prolong life span or grow hair on a bald head?

5.1 For the same reason that it was worthwhile to climb Mount Everest or to go out to Antarctica or in space. There would be benefits that are obvious today, but there would be many more that are not so obvious today. Ideally, the complete genome should be sequenced, for what is not expressed is not necessarily unimportant or totally non-functional (expression may not be the only function of DNA sequences).

5.2 Incalculably more. It would revolutionise biology, as determination of the structure of DNA did.

5.3 Both are equally important in their own way. In some cases environment may have no influence on the expression of gene; in some other cases, all the influence.

5.4 First question: A great deal is understood, though the final word has not been said: it may indeed be never said. Second question: Possible but unlikely.

5.5 Not in India. I don't know about Britain, the best person to answer this question for Britain may be Sir Walter Bodmer, FRS.

6.1 Many pieces of evidence. For example, reduction in the frequency of carriers of sickle-cell haemoglobin gene in the black population in the US over the years they have been in the US.

6.2, 6.3 and 6.4 There are bound to be important consequences. And we need to learn to predict them. For example, our ancestors could fight well and freely, with probably no less agility, with 50 kg of armour on them. How many can do that today?

6.5 Would depend on the extent to which these are practised.

6.6 Only quantitively and in terms of specificity, not qualitatively. The difference would be like having four aces in one deal out of a 100, and having four aces in the same hand in 95 deals out of a 100.

6.7 How is clinical interference any different than interference by man-made or generated factors that have always influenced human behavioural drives!

Memorandum by Janice Wood-Harper (HGC 137) (27 March 1995)

THE "SPECIAL" NATURE OF GENETIC INFORMATION: THE AUTHOR'S POSITION

SUMMARY OF THE POSITION

The distinction between genetic and other medical information cannot be made solely on the basis of qualitative differences despite the significance of their synergistic effect in contributing to genetic testing being viewed as a revolutionary technique for medical diagnosis and prognosis.

The distinction lies rather in the way in which genetic information is generally perceived as having a more precise and thus scientifically sound basis; the complexities surrounding its accurate interpretation; and its unique and powerful influence on changing society's concepts of "healthy" and "diseased" states and also its attitudes towards those who are found to have genetic disorders.

THE POSITION IN SUPPORT OF CONFIDENTIALITY ISSUES RELATING TO GENETIC INFORMATION BEING NO DIFFERENT TO THOSE RELATING TO OTHER FORMS OF MEDICAL DATA

It is inconsistent to prohibit or restrict access and use of genetic data when there are no similar limitations applied to other medical data since there are only relative differences between genetic information and other medical information and no absolute ones.

Genetic tests yield information which differs only *qualitatively* from other medical data.

Genetic tests facilitate improved standards of diagnosis and provide more reliable and accurate prognostic information for a wider range of diseases.

Genetic information has more definite implications for relatives and future progeny; its likely future proliferation will implicate a larger proportion of society and therefore augment current problems concerning misuse of medical data.

Most, if not all, current medical data which is legitimately accessed and used by interested third parties for making distinctions between individuals has, to at least some extent, a genetic component.

The severity of the consequences of misuse of genetic information, particularly in terms of violation of human rights, is the same as from that resultant from the misuse of other types of medical data.

THE POSITION IN SUPPORT OF GENETIC INFORMATION BEING TREATED DIFFERENTLY FROM OTHER TYPES OF MEDICAL INFORMATION AND, SPECIFICALLY, OF THERE BEING MORE STRINGENT CONTROLS TO ENSURE CONFIDENTIALITY OF GENETIC INFORMATION

Genetic testing will result in the unprecedented proliferation of information of a highly personal nature.

Storage of vast quantities of genetic information on data bases will seriously exacerbate problems currently experienced with maintaining privacy of medical information.

As there are no absolute differences between genetic information and other types of medical information, any justification for genetic information constituting a special case for consideration becomes partly dependent upon the strength of the argument as to whether its qualitative features are *sufficiently* distinctive and/or whether the potentially damaging consequences of its misuse are *sufficiently* serious.

Genetic testing can be distinguished on the basis of the *combined* effect of a number of factors, such as its independence of age, clinical state and tissue type and size of sample.

One of the most significant features of genetic testing is its ability to yield predictive information about susceptibility to disease and information relating to carrier status in asymptomatic individuals.

Innovations in prognosis made feasible by genetic testing is likely to be influential in changing both professional and public perceptions of the "diseased state" and also therefore attitudes towards affected individuals. Such testing might, in turn, give rise to a new basis for making distinctions between individuals and consequently affect the ways in which they are differently treated.

In theory, genetic testing could reveal that each and every individual has some genetic disorder which, to a greater or lesser extent, confers susceptibility to a genetically-influenced condition. Because of this universality, genetic testing is likely to bring about reclassification of many individuals, formerly regarded as "healthy", as "unhealthy" or "genetically-ill".

It is probable that predictive genetic information will necessitate complex decisions as to choice of criteria, that is the type and level of susceptibility, which might justify an individual being labelled as "abnormal". This situation is likely to result in increasing numbers of individuals being assigned to a "biological underclass" and being subjected to differential, or discriminatory, treatment. At their most extreme, repercussions might include an upsurge in eugenic policies or revision of justifiable grounds for euthanasia.

Genetic information is intensely personal in that (with the exception of identical siblings) it is unique to each person. This, in itself, means that it is more likely than medical information of more general application to lead to stigmatisation of individuals.

The possibility of widespread predictive information bringing about modification of classic definitions of "health" and "disease" might imply that a distinction between genetic and other medical data rests on whether genetic explanations of disease, and their interpretation in terms of what might be perceived as diseased or healthy conditions, are in some way more powerful than traditional medical explanations.

Accurate interpretation of complex genetic information requires expert knowledge. There is a danger, at least in the shorter term before educational programs for both professionals and non- professionals are initiated, that such information will be accessed and used by those who are not adequately qualified to analyse it or assess its implications for the health of test subjects.

The potential severity of the consequences of decisions which are based on such misinterpretation is immense. Misconceptions about genetic data might lead to adverse nonclinical outcomes, such as unfair discrimination against individuals manifested, for example, in the denial of social entitlements.

Public awareness, opinion and attitudes are strongly influenced by the mass media and its role in communicating information about genetic discoveries. Although geneticists acknowledge that the predictive value of genetic tests is likely to remain poor, it is probable that non-experts, including the general public, will perceive the new genetic explanations as representing absolute truths.

The significance of this situation might be the acceleration of a movement towards a more socially constructed perception of illness.

Outcomes of genetic research are frequently presented to the public in a way which promotes a deterministic and reductionist approach to disease. The inherent danger is that non-experts will increasingly come to believe that all human conditions of health and disease, or alternatively the characteristics which distinguish one individual from another, can be explained in terms of "genetics".

The strength of belief in genetic determinism reflects society's desire to find a simpler solution to social problems which is not dependent upon social reform or changing individual behaviour.

Public perception of "genetics" is a significant factor in distinguishing the social implications of genetic information from other medical data.

Until such time as the general level of education about genetic principles is improved, then this is likely to be the most influential factor in determining how the new genetic knowledge is applied in society; the extent to which it is used for medical benefit or to the detriment of both individuals and society as a whole.

THE "SPECIAL" NATURE OF GENETIC INFORMATION: AN ARGUMENT

Introduction

This article takes the view that, at least in the shorter term until there is a higher level of general education about genetic principles, information emergent from new genetic tests about an individual's genome should be regarded as confidential. It supports the need for policies to ensure that privacy of genetic information is safeguarded by prohibiting access to such information by interested third parties, such as employers and insurers, who might use it for discriminating between individuals with adverse social consequences.

In order to justify such action, it is necessary to clarify the special features inherent in genetic information which distinguish it from other medical information produced by more traditional methods of testing. Although both types of information might potentially be used to make distinctions between individuals, the latter, in general, is not thought to justify protective policies to safeguard against its misuse.

The argument initially identifies the problems which are encountered in attempting to differentiate between information resulting from genetic testing and that gained through conventional medical tests. It then presents the view that the combination of several features, which in isolation do not represent absolute differences, contributes to genetic information being regarded as "special" and therefore requiring different regulation. Particular emphasis is placed on the significance of the potential for misinterpretation of genetic information and public perception of genetic explanations in influencing classic definitions of "health" and "disease" and therefore attitudes towards those found to have genetic disorders.

Difficulties in distinguishing genetic information from other types of medical information

An argument in support of the view which disputes the need for specific policies to safeguard against the misuse of genetic information, is that the severity of the consequences of misuse of genetic information is no different from that resultant from the misuse of other types of medical data.

> Genetic prophecy for all its modernness and mystery presents us with the same challenges as old-fashioned tests: the results can be put to purposes which jeopardise human rights (Artherley, 1983: 273).

When attempting to justify the need for special consideration to be given to the use of genetic information, one particular obstacle is commonly encountered. As Gevers explains:

> When genetic testing is seen as a form of medical testing (although not just another form), the extent to which the use of genetic data is possible depends first of all on what is allowed as to medical selection in general. Furthermore, if there are only relative differences between genetic information and conventional medical information and no absolute ones, it will be very difficult to argue that the use of genetic data should be prohibited when the use of other medical information is not subject to any limitations at all, the more so since at least part of the conventional medical data used for selection purposes are likely to be related to a person's genetic make-up (Gevers, 1993: 129).

This argument can be defended from the standpoint that genetic tests yield information which, although of a special nature, differs only qualitatively from other medical data. For instance, genetic tests can be viewed as advanced tools which facilitate improved standards of diagnosis compared with alternative medical tests and also provide more reliable and accurate prognostic information, at least for some genetic disorders, as to risk of developing disease compared with traditional methods which rely on data from family pedigrees.

Other distinguishing qualitative features of genetic information have been identified as: its present immutability (although gene expression might be significantly affected by environmental factors) and therefore its relevance throughout life; its implications for relatives and future progeny and the increased potential for discrimination through its ability to reveal other personal traits, such as ethnicity and race; the increased social stigma which is associated with genetic traits for serious disorders (Billings, 1993: 36; Gevers, 1993: 127). Additionally, once they become more widely implemented, genetic testing and screening will result in a vast proliferation of information which, by potentially implicating a large proportion of the population, will bring about concomitant augmentation of problems currently inherent in the misuse of medical data.

The combined effect of qualitative differences inherent in genetic information

It would seem that, if a distinction is to be made, it does not rely upon any unique property of genetic testing. Harper (1992:184) suggests that the difference lies in the combining force of several factors, such as the independence of genetic testing on age (it can be performed at any stage of life from conception, *or even pre-conception,* into old age); clinical state (whether or not symptoms are currently manifested and their degree of severity); and tissue type (genetic disorders can be detected in all DNA-containing cells regardless of their functional state) and also the stability and small scale of sample.

Predictive

One of the most significant factors is possibly the predictive nature of genetic information. Indications for conventional medical tests are usually provided by currently expressed symptoms of disease and individual susceptibilities to disease have been largely based upon methods which depend upon knowledge of family medical histories demonstrating a propensity to a particular inherited condition. It has been long established, for instance, that diseases, like cardiac heart disease, breast cancer and Alzheimer's disease, have a familial component (Harper, 1992:184). Genetic testing is already revealing disorders, like carrier status or predisposition

to late-onset disease, in asymptomatic individuals and, with progress in identification of genes which contribute to polygenic conditions, will increasingly enable predictions to be made about susceptibilities to a wide range of these common diseases. Because it is probable that every individual has some susceptibility to disease (they only differ in the extent of that susceptibility), testing is likely to result in many people, formerly regarded as "healthy", being reclassified as "unhealthy" or "genetically-ill". This innovation in prognostic ability could well be influential in changing both professional and public perceptions of the "diseased state" and also therefore attitudes towards affected individuals. Such testing might, in turn, give rise to a new basis for making distinctions between individuals and consequently affect the ways in which they are differently treated.

Personal

This problem is compounded by the fact that genetic information is intensely personal in that (with the exception of identical siblings) it is unique to each person. This, in itself, means that it is more likely than medical information of more general application to lead to stigmatisation of individuals.

> Prejudice, alienation and exclusion often accompany genetically related diseases, even though, by definition, the condition is neither subject to the person's control, nor the result of willful behaviour (Gostin, 1991:110–1).

Identification of susceptibility

It is likely that genetic research will eventually demonstrate that susceptibility to disease is universal. Although it is conceivable that this might reduce, for instance, stigmas associated with certain diseases, it is also possible that varying levels of personal susceptibility might necessitate decisions as to the degree of susceptibility which would justify subjecting an individual to a particular action or treatment as the result of him being perceived as "different". In other words, the situation might raise questions relating to whether or not those with certain predispositions to genetic disorders should be labelled as "abnormal" and the choice of criteria which would be relevant in reaching such a decision.

> What is to be defined as normal or abnormal? And whose yardstick should prevail? In all, we risk increasing the number of people defined as unemployable, uneducable, or uninsurable. We risk, in other words, creating a genetic underclass (Nelkin, 1992:190).

In addition to the above examples, identified members of a "genetic underclass" might be treated differently in a variety of other ways. For example, it might be considered that fetuses which have high susceptibility to serious conditions should not be allowed to be born, thus increasing the range of disorders for which abortion is thought to be justified and furthering a move towards eugenic policies. It might be argued that euthanasia is appropriate for individuals found to be predisposed to incurable late-onset disease and who are unable to deal psychologically with such information. Also, in a situation of limited health resources, access to costly health care for patients with high susceptibility might be restricted.

It is necessary at this point to return to the original question of what is it that distinguishes genetic information from other medical data. the crux of the problem rests with there being no absolute differences. Therefore any justification for genetic information constituting a special case for consideration becomes dependent upon the strength of the argument as to whether its qualitative features are *sufficiently* distinctive and/or whether the potentially damaging consequences of its misuse are *sufficiently* serious.

The preceding discussion has identified several qualitative differences but it is doubtful whether these, by themselves, are adequate to justify special regulations in respect of the use of genetic information. The suggestion was made that an increase in predictive genetic information might result in the modification of classic definitions of "health"and "disease". This implies that a distinction between genetic and other medical data might rest on whether genetic explanations of disease, and their interpretation in terms of what might be perceived as diseased or healthy conditions, are in some way more powerful than traditional medical explanations.

The significance of genetic explanations and their interpretation

Genetic research is now beginning to provide answers to questions which have long eluded the medical community. Together with advances in biotechnology, it is enabling revolutionary understanding and treatment of many diseases; their aetiology; and modes of inheritance. Whereas in recent years there has been trend away from primary reliance on palliative medicine towards more preventive measures, particularly in relation to common diseases like heart disease and cancers, research is providing more conclusive evidence in support of specific genetic components being at least partly responsible for individual susceptibility to such diseases. Although it is acknowledged among genetistis that the predictive value of genetic tests, particularly for multifactorial diseases, is likely to remain poor (Cook-Deegan, 1991: 63; Council on Ethical and Judicial Affairs, 1991: 1827; MacKay, 1991: 248), there is every likelihood that, beyond the confines of this discipline, the general public will come to perceive the new genetic explanations as representing absolute truths.

It is likely that misconceptions will be largely augmented by the power of the mass media which, in forming the main vehicle by which information regarding new genetic discoveries will be imparted to the public at large, will play a vital role in influencing awareness, opinion and attitudes. The significance of this situation might be the acceleration of a movement towards a more socially constructed perception of illness. Support for this speculative view was provided by the extensive press coverage in July 1993 of research finding "hard evidence" of a "gay gene" and subsequent discussion about the implications of this discovery (Connor, 1993; Ridley, 1995). There has also been recent debate on the genetic basis of criminality (Patel *et al.*, 1995). Both of these examples also illustrate the danger of presenting a view of genetic research which encourages a deterministic and reductionist approach to disease. In explaining the concept of what she terms "geneticisation", Lippman states:

> . . . the dominant discourse describing the human condition is reductionist, emphasising genetic determination. It promises scientific control of the body, individualises health problems and situates individuals increasingly according to their genes. Through this discourse, which is beginning seriously to threaten other narratives, clinical and research geneticists and their colleagues are conditioning how we view, name and propose to manage a whole set of disorders and disabilities. Though it is only one conceptual model, "genetics" is increasingly identified as *the* way to reveal and explain health and disease (Lippman, 1991: 18).

It is probable that the majority of the general population, who do not have a basic knowledge of genetic principles, will accept as true the reductionist images of genetic explanations presented by the media. The goals of genetic research have been termed "The Holly Grail" in the search for what it is that makes us human (Watson, 1990: 44; Suzuki and Knudtson, 1990: 316-7); providing enlightenment on hitherto unexplained human conditions and possibilities for the ultimate eradication of disease. To view genetic knowledge as being able to supply the ultimate solutions to questions concerning the factors which contribute to making human beings different from each other indicates, however, a lack of appreciation of the complexities of human characteristics. As Billings states, in relation to complex traits such as sexuality or criminality:

> . . . descriptions of human characteristics relying solely on genetic data will always be too simplified and reduced. More generally, it is self-evident that we are more than the sum of our genes and should never be slaves to our DNA (Billings, 1993; 35).

Nevertheless human nature is such that people generally have an innate desire to be provided with uncomplicated and absolute solutions to problems. When these solutions are supported by so-called "scientific evidence", there is a tradition of them being received by the public largely without question. Wertz supports this concept by proposing that:

> Many people, especially those who suffer from so-called behavioural problems, would be overjoyed if scientists found a genetic cause for these problems, because this would remove the personal and family stigma attached to behaviour disorders . . . Further, many believe that it will be easier to cure a genetically-based problem . . . than to try to treat a social problem or to change individual behaviour. So to sufferers and their families, "genetic determinism" may actually be a liberating release from individual responsibility (Wertz, 1992: 502-3).

Shuster stresses the significance of public perceptions about genetics and the dangers which could result:

> A perception that human genetics is essentially deterministic and reductionist could lead to the misapplication of genetic information and foster socially dangerous ideologies . . . the perception has been that what is genetic is unchangeable, and that problems of criminality, behavioural deviation, individual capability, even differences between sex, race and general individual capability, even differences between sex, race and general intelligence (IQ) can be accounted for solely from within the domain of human genetics. Ultimately, perception is all that matters. If it cannot be persuasively dispelled, the applicability of genetic information in predictive and curative medicine and in practical human affairs will be problematic at best and curative medicine and in practical human affairs will be problematic at best and could be dangerously attractive and destructive of cultural and moral interests (Shuster, 1992: 116).

Until such time as more emphasis is placed on widespread education about genetics, for both professionals and the general public, via the public educational system and other channels of learning, misconceptions about genetic information are likely to continue and proliferate. This will undoubtedly lead, at least in the interim period, to misuse of such information and diverse harmful social consequences.

Summary

The distinction between genetic and other medical information cannot be made solely on the basis of qualitative differences despite the significance of their synergistic effect in contributing to genetic testing being viewed as a revolutionary technique for medical diagnosis and prognosis. The distinction lies rather in the way in which genetic information is generally perceived as having a more precise and thus scientifically sound basis; the complexities surrounding its accurate interpretation; and its unique and powerful influence on changing society's concepts of illness and also its attitudes towards those who are found to have genetic disorders.

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Letter to the Committee Assistant from Dr Paul Debenham, Managing Director of University Diagnostics Limited (HGC 138) (28 March 1995)

Re: CYSTIC FIBROSIS GENE TEST SERVICE

Thank you for your letter of 6 March 1995 concerning the Science and Technology Committee's interest in the new Cystic Fibrosis gene test service offered by University Diagnostics Ltd (UDL). I will endeavour to address the issues you raise in this letter. For your reference I also enclose some samples of literature associated with the service.[1]

[1] Not printed.

The Cystic Fibrosis (CF) Test—a logical progression for UDL

UDL, established in 1988 in part by University College London, has from its inception focused on biotechnology-based diagnostic services. Since 1992 the Company has specialised in just one area of its expertise, that of DNA diagnostics. The Company offers a paternity testing service with Registered Paternity Testers (Lord Chancellor's office) involving DNA tests used by the public at large. UDL also provides the DNA testing services for the Foreign and Commonwealth Office's immigration casework, acts for the Defence in the examination of DNA forensic evidence and offers a genetic marker analysis service for livestock breeders. UDL is therefore well versed in the provision of genetic test services whose outcome can have a major personal impact on those involved. UDL is accredited to BS5750 (ISO 9002) for these services, and compliance with this Quality Standard requires a strong focus on client expectations. With this experience the Company has naturally considered offering medical diagnostic genetic testing services when such services become feasible and appropriate.

CF gene diagnostics—a private health care issue

Each human disorder will have its own unique set of characteristics which will determine if it is both acceptable and viable to be the subject of a commercial genetic diagnostic service. Such a judgment is presently not subject to external regulation, it is a matter for each Company to determine.

UDL has determined that CF diagnosis is acceptable for several reasons. Population screening for CF has been the subject of numerous studies and reviews since 1991 which conclude that technically such a service is feasible. The psychological impact of receiving the results of such tests is variously interpreted but, in general, information learnt by a client can be understood, and benefitted from, if appropriately advised both before and after taking the test. The clients will not be learning of an adverse factor in their own personal health, but rather of that which a future child might inherit. 95 per cent of clients will learn probably, to their relief, that they have a minimal chance of having a child affected by CF, whilst couples learning that both partners are CF carriers can progress into pregnancy with advised foresight. The process of identifying the CF status of a foetus for such individuals can be readily achieved by a Chorionic Villus Sample test which is relatively routine nowadays.

UDL believes this CF diagnosis service will be commercially viable firstly because the published studies indicate a desire by the public to know their CF status once they have been informed about the disorder and secondly there is a high prevalence of CF carriers in the UK. This CF carrier diagnosis is not available through the NHS unless you are a relative of an identified CF Carrier. Understandably a commitment to population screening would represent a major drain on NHS funds. UDL believes it can offer the test, with appropriate counselling, at a price that is very small in proportion to the total financial commitment a couple take on when starting a family. UDL is making available the choice of a CF diagnosis for peace of mind or advised foresight, as an option for couples in the planning of parenthood.

CF gene diagnosis—criteria for the service

There are no legal regulations, to my knowledge, specifically determining the nature of any genetic testing service within the NHS or in the private health care sector.

In 1987 the establishment of the UK's first DNA fingerprinting service for the determination of parentage and forensic evidence, by ICI, was established and accepted by academic acclaim alone. Legal recognition of the findings took a further two years to be enacted. At that time I was personally involved in the definition of that service as the Director of Scientific Services for the ICI subsidiary involved. Then, as now, the principle determining the nature of a genetic testing service in the private sector has been that of pro-active self-regulation. Unacceptable services gain critical media attention which in the private sector must be addressed or the business will fail.

UDL has waited until a highly validated CF test was established academically and was available for commercial usage. In this manner the scientific credentials of the test are beyond reproach. In fact I personally was involved in initiating trials of this diagnostic test (for ICI) with the Cystic Fibrosis Research Trust in 1991 and with leading European CF research scientists in 1992. To date this test technology has been trialed on over 40,000 individuals and became formulated as a quality controlled test product from Kodak Clinical Diagnostics for use in a diagnostic service in November 1994.

UDL determined that it should provide, prior to the test, a simple but informative leaflet about CF along with an informative letter about the appropriateness of the test, how the test is performed, and how counselling would be provided. These would be sent to a potential client or couple (see next section). The drafts of those texts and the detail of the proposed service were developed in a consultation process with two external sources of CF expertise.

Foremost was the Cystic Fibrosis Trust. The CF Trust is pre-eminent in the field of CF experience and counselling. I therefore asked the Trust's Medical and Scientific Administrator, Dr Martin Scott if he would review all our texts, documents and service outline for advice and guidance. The Trust has been extremely helpful in this respect and UDL have incorporated all advised changes. The CF Trust's advice was not compulsory, and as a charity it cannot actively approve or accredit a commercial service. However if the CF Trust actively disapproved of any CF service, I would expect that service to be rapidly discredited and cease.

UDL's second source of advice has been Dr Martin d'A Crawfurd MB, BS FRCPath who is a private Clinical Genetics consultant and was formerly the senior consultant Clinical Geneticist at the Kennedy Galton Centre. Dr Crawfurd acts as UDL's counselling consultant for our CF gene diagnostic service. Dr Crawfurd will advise the client by phone or at a face to face consultation as required by the client; this service is included in the fees charged.

Both experts have also advised on the nature of our reports back to the clients and in fact we provide a booklet obtained from the CF Trust to CF carriers as part of our information package (see below). It was felt that the client could choose to participate in the CF test totally independently of their GP (unless pregnant) or could opt to receive the results via their GP if the GP would consent to help in this way. This latter option is similar to Down's Syndrome testing that can be privately paid for with the results being communicated by the GP. The GP acts solely as a professional conduit for relaying the results. Specialist genetic counselling is still provided by UDL's Clinical Geneticist Consultant. UDL believes this service addresses the needs of the clients with respect to providing appropriate counselling support.

If aspects of our service are not found to be satisfactory then it is a requirement of our BS5750 (ISO 9002) accreditation that we improve our service to retain this Quality Standard. A Company must be very client focused to meet and maintain this accreditation; all clients' complaints must be recorded and the service adjusted to improve unsatisfactory services. If UDL fails to meet our clients' perceived needs the Company will fail its accreditation audits. No regulation requires a genetic testing service to be registered to BS 5750 (ISO 9002), but it is becoming a standard quality requirement in commercial diagnostic contracts.

UDL's CF gene diagnostic test service

Accompanying this submission[1] I append samples of the various documents that UDL provides to clients through the course of the testing service. These documents explain the service and the results:

(i) A leaflet providing information on CF and UDL's test service. This is sent out to all our potential clients.

(ii) An information letter sent to non-pregnant individuals outlining their options with respect to participating in this test.

(iii) An information letter sent to pregnant individuals interested in taking this test.

(iv) Information sent to clients to explain how to provide a mouth wash sample in the privacy of their homes.

(v) An example of a CF carrier negative result package sent to the client or their GP.

(vi) An example of a CF carrier positive result package sent to the client or their GP (including the CF Trust booklet).

The CF gene test service—take up rate

UDL's CF gene diagnostic service was launched in December 1994. Despite media interest there has been little public uptake to date. UDL is presently working to inform clinics, laboratories and consultants in the private healthcare sector about this service. This is leading to a small number of samples being received. When the process is complete we will consider how best to better inform the public and GPs about CF and our test service. Therefore the uptake of tests is expected to gradually increase over the next six months at least.

Further Information

I hope I have provided the Science and Technology Committee with suitable information for its consideration. I will readily provide further information, or attend the Committee to discuss any questions it might have.

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[1] Not printed.

Memorandum from Georges B Kutukdjian, Director Bioethics Unit, UNESCO (HGC 139) (22 March 1995)

GENETICS AND HUMAN RIGHTS

I. Introduction

In the early 90's on several occasions the General Conference of UNESCO emphasised "the ethical implications of scientific experimentation and technological innovations, actual or potential" in fields such as molecular biology, genetics and biomedical sciences.

In 1993, the Executive Board of UNESCO stressed "the need to develop information exchanges and to carry out extensive consultations within an intercultural framework, in order to precisely identify the issues involved in the control of the human genome".

These decisions led Mr Federico Mayor, Director-General of UNESCO, to create the International Bioethics Committee (IBC—the first institution of its kind in the world—so as to examine the ethical, socio-cultural and legal questions raised by research in genetics and their applications. He invited some 50 eminent biology, genetics, medicine, law, philosophy and social and human science specialists, including four Nobel Prize winners, to become members of this Committee which is chaired by Mrs Noëlle Lenoir, Member of the French "Conseil Constitutionnel".

II. Aims of the International Bioethics Committee

The action engaged by the IBC is three-fold. First, it is conceived as a forum for the exchange of ideas and debate on the ethical, legal, social, and, more broadly, cultural implications of genetic research and their applications. Second, the IBC promotes action aimed at enhancing the participation of the public in this debate. This action takes the form of educational and informational activities addressed to decision-makers, professionals particularly concerned and the public at large. Third, the General Conference of UNESCO, at its 27th Session, requested *"the preparation of an international instrument on the protection of the human genome"*.

The IBC has many potential tasks, from providing information to suggesting principles for international legal recognition. In its ethics evaluative role, the principles and materials of international human rights law may yield a rich supply of doctrines.

The Universal Declaration of Human Rights and the two International Covenants on Human Rights demonstrate that from certain internationally accepted principles one can derive those that apply to human genetics.

- The respect for human dignity and worth.
- The right to equality before the law.
- The protection of rights of vulnerable individuals.
- The right not to be subjected without free consent to medical or scientific experimentation.
- The right to the highest attainable standard of physical and mental health.
- The right to protection against arbitrary interference with privacy or with the family.
- The right to enjoy the benefits of scientific progress and its application; and
- The right to freedom of scientific research.

III. Genetic research

Spectacular advances in the fields of molecular biology and genetics allow man to fathom the very essence of the living and to have a better knowledge of the processes of programming, differentiation, repair, renewal and decay of living beings, without however being able to master the mechanisms as yet.

Genetic research has passed an important milestone with the convergence of molecular biology, data processing and robotics. For approximately the last four years, this convergence has permitted the physical and genetic mapping of genomes on a vast scale. Genome sequencing remains the indispensable tool for locating and identifying the genes involved in illnesses, such as hereditary diseases or certain types of cancer, that have a genetic factor.

Several ethical questions arise in this connection:

- The definition of the status of fundamental knowledge about the genome: the controversy on the

patenting of partial DNA sequences underlines the urgency of providing compatible international solutions, in the absence of which certain research work can be disrupted.

— The risk of labelling genes as "good" and "bad". This should in no case constitute a basis for stigmatising an individual or a group.

IV. Genetic screening and testing

Following the identification of a gene and the genetic sequence responsible for an illness, a genetic test is developed and provides a means of detecting the presence of the illness in an individual. In this field, ethical considerations have spawned many debates. The same holds true for prenatal genetic diagnosis, the development of which has accelerated in many countries.

Genetic screening to date has been applied to relatively rare conditions. However, recent research has begun to clarify the genetic basis of many cancers and heart diseases. Events have confirmed an estimate, given in 1990, that by the year 2000 genetic factors would have been uncovered for roughly one-quarter of cancers and heart diseases. This decade therefore presents us with the challenge of facing the implications of genetic screening for common diseases.

The second facet of recent research developments is that our knowledge, hitherto confined, to some 4,000 monogenic diseases, is now expanding to include multigenic and, more importantly, multifactorial conditions (multifactorial conditions are those where the genetic element shows as a predisposition).

Hence, genetic diagnosis updates ideas about *medical prevention.* It is capable of providing the latter with the efficiency it often lacks, but ambiguously so. No doubt in terms of *individual prevention,* the fact that an individual can know his or her genetic predispositions can lead to a more responsible attitude. It can incite him or her to adopt behavioural patterns which could prevent the onslaught of illness.

Genetic screening may be regarded as a matter of public health policy. It follows that the state should assume certain responsibilities (the executive responsibility for these matters may, in certain cases, be delegated to professional bodies or to bodies with a high proportion of professional membership). These responsibilities include the following:

(1) Ensuring that genetic screening and testing is *restricted to conditions that seriously affect the health* of the individual. Genetic screening and testing may be particularly appropriate to those conditions that result in early death;

(2) Exercising great care in initiating screening programmes and testing for *late-onset diseases.* It will usually be appropriate to screen for those late-onset diseases for which preventive treatment is available. In most such cases, it is *unlikely to be appropriate* for any testing to be done before adulthood;

(3) Ensuring that *adequate information* is available to the person being screened or tested;

(4) Ensuring the *informed and free consent* of the person being screened or tested;

(5) Provision of *appropriate support and/or counselling* for those being screened and tested and for their families, where this is appropriate;

(6) Ensuring the maintenance of *medical confidentiality.* This is no easy task in the face of the growing tendency to store medical information in computable form;

(7) Protection against the *misuse of genetic information by third parties.* Experience in some countries has already shown that problems may be raised in connection with *employment* and *insurance;*

(8) Ensuring *equitable access* to genetic screening and testing.

The threat of abuse of genetic screening requires safeguards. Public understanding of human genetics should create awareness of the dangers both of eugenics and of the possible stigmatisation of those carrying or suffering from genetic disorder. This need for an understanding of human genetics should be borne in mind by those responsible for the educational curriculum and for public health education.

V. Gene therapy

Even more recent than genetic testing, gene therapy provokes equally as much wonder and worry. *Somatic or germ-line therapy* consists of introducing into the affected cell a working gene, i.e. one which is capable of correctly coding in the place of a deficient gene of one whose expression is anarchic.

Somatic gene therapy alters the DNA of the body's differentiated cells, that is, cells that lack capacity to transmit genetic material to offspring, whereas germ-line gene therapy changes the DNA of reproductive cells.

Gene therapy has been experimented on somatic cells, for rare diseases such as adenosine desaminase deficiency (ADA), for cystic fibrosis, or to treat certain cancers such as malignant melanoma or lung cancer. In the future somatic gene therapy could be frequently used to treat other cancers as well as HIV-infection, rather than the inherited single gene disorders.

In the ethical controversy caused by experimentation with gene therapy, several issues stand out clearly.

First, precautions have to be taken with *somatic gene therapy* in that the treatment is totally experimental comprising risks as yet inadequately measured. In as much as all present gene therapy constitutes medical and scientific experimentation, (and a rather extreme form of it), the right not to be subjected without free and informed consent to it should be guaranteed.

Recent gene therapy discussions insist that somatic cell procedures should be reserved for "serious disease", because of the highly experimental nature of procedures, and the lack of sufficient experience for determination of the incidence and seriousness of side-effects that accompany various types of cellular alterations.

Another major subject of controversy relates to *germ-line therapy*. Enormous technical problems would have to be solved to make the technology realistic in light of the risks, particularly the control of gene expression throughout the organism's process of cellular differentiation. No human germ-line interventions can be safely developed without the opportunity to test whether genes, inserted in the reproductive cells or in the zygote, are replicated appropriately in the first stage of cellular differentiation.

An agreement (albeit provisional) seems to have been reached prohibiting recourse to this therapy as long as the scientific data enabling its control is unavailable, and consequently, as long as it comprises risks of uncontrolled alteration of the human genetic capital.

The following conclusions can, at present, be reached:

(1) *Somatic cell gene therapy is permissable,* regulated as an experimental therapy.

(2) *Its use for enhancement purposes may be widely prohibited,* but it should not be categorically disapproved as unethical in all imaginable circumstances.

(3) *Germ-line interventions are indefensible at present,* but they should not be categorically disallowed.

(4) *The use of germ-line interventions for enhancement purposes should be categorically prohibited.*

One final area of discussion concerns a *world view of the existing and potential therapeutic spin-offs of genetic research.* It would not be in keeping with ethics to reserve the benefits stemming from genetics solely for industrialised countries. This is why there is an urgent need to define the orientations of a policy to promote these therapies for the benefit of developing countries. The difficulties facing any such policy are far from negligible, however. Can *gene therapy* be reasonably implemented in developing countries? How can developing countries benefit from the input of *drugs deriving from genetic engineering,* whose potential seems staggering? While *vaccines produced by genetics* are likely to provide a satisfactory therapeutic response for a whole range of illnesses spread all over the surface of the globe, like malaria or AIDS, the means to manufacture and distribute them have yet to exist.

VI. Conclusions

A Preliminary Outline of a declaration on the protection of the human genome has been drafted by the International Bioethics Committee (copy attached). It embodies the on-going debate regarding human genetics and human rights. It aims at striking a balance between the benefits for mankind of the achievements of genetics and the respect of human rights and fundamental freedoms. It stresses freedom of scientific research and the rights and obligations of researchers.

Memorandum from the Newman Association—Bio-Ethics Committee, (HGC 143) (4 April 1995)

Introduction

Catholic teaching holds that science must be at the service of man who is the only creature that shares in the life of God and is made in his image. From this flows a unified view of human dignity, sanctity of life and values that are especially relevant to health care and related sciences.

We will therefore respond to the Committee's six key questions set out on page 1 of their document "Human Genetics" of 3 November 1994. Where our response is relevant to the other specific questions on pages 1-3, we will indicate the relevant question in parenthesis.

THE CURRENT STATE OF THE HUMAN GENOME PROJECT

Genetic diagnosis based on the sequencing of the estimated 100,000 genes will assume greater importance over the next five years. The human genome is being mapped and by or before the year 2000 the disease-risk profiles of individuals will be discernible. It will be possible to predict diseases before they are manifest. As well as being used diagnostically the new genetics will shift the focus towards prevention and prediction.

As living processes are understood increasingly in molecular terms, new possibilities for pharmacology will follow a newer and more fundamental understanding of disease. It will also make interventions at molecular level possible by *somatic* and *germline* gene therapy. These developments will confront science with difficult ethical, economic and social questions. Some of these will need to be addressed by legislation.

Society will have to give legal sanction before germline interventions are permitted (1.5). This is one area of research which should be prohibited at present.

As the new genetic knowledge becomes available it will first be used in population screening and, where risks are deemed to justify it, in ante natal screening. Existing law does not justify abortion for such treatable diseases as diabetes and we feel that there is a case for the existing law on abortion to be amended to make it clear that this is so. More thorough counselling is required (3.4) and the present opt in protocols for ante natal diagnosis should not be changed to opt out programmes.

The moral problems posed by near universal ante natal screening to conscientious objectors to abortion and certain cultural and ethnic groups opposed to abortion are not adequately considered. (The very absence of this question from your list illustrates a certain blind spot to one of the problems of ante natal screening.) We continue to defend stoutly the right of mothers-to-be not to be subjected to unwanted ante natal screening.

Economic imperatives may move research from "predict and prevent, or diagnosis and treat, to test and abandon".[1]

Patients would then increasingly refuse tests as has already been shown.[2]

Somatic gene therapy is now taking place under arrangements laid down in the *Report of the Committee on the Ethics of Gene Therapy (Clothier 1992)* where treatment/research is confined to a few centres with both local and national ethics committees' approval. This arrangement still lacks statutory control which should now be brought in. Undue weight should not be given to patenting or commercial considerations (4.3).

THE DRIVING FORCES BEHIND SCIENCE

The search for knowledge where experimentation concerns man should be subject to the constraints of the Helsinki Convention where the interests of the subject take precedence over those of science or society. There are two other driving forces behind the current genome research and they are commercial considerations and health care economics. The latter is linked to public acceptance and education and the rationing of limited resources. At present this rationing is set by gate keeping and waiting lists. In the USA it is regulated by medical insurance whereas in Germany there is agreement with doctors for basic provisions which can be supplemented by additions purchased by individuals. Similar developments are likely to take place in this country (4.3) in the face of an aging population.

BENEFITS AND OTHER CONSEQUENCES OF RESEARCH

There will be victims of screening programmes if it is undertaken without adequate ethical constraints and counselling. These include stigmatisation, discrimination, implications for procreative freedom, psychological trauma, and an impact on self esteem. There is a possibility for misuse, misappropriation and eugenics.[3] Insurance and employment discrimination has occurred and there is pressure for abortion and a consequent effect on adoption rights. A new genetic underclass termed the "asymptomatic ill" has been described.[4]

Catholic organisations in this country have recommended that all genetic information should be the exclusive property of the individual.[5] The current privacy laws are not adequate and we do not agree with the RCP report "Ethical Issues in Clinical Genetics" 1991 that genetic information could be disclosed to family members with consent. Almost everyone has some genetic predisposition to disease and the pure human genome is a myth.

Screening programmes should be confined to readily curable diseases like phenylketonuria, or the invariably lethal and incurable diseases like Huntingdon's Chorea. Otherwise screening will produce more suffering. Proxy consent for minors should be particularly circumscribed, whilst adult screening for treatable diseases, such as for the breast cancer gene, may be justified where there is a strong enough family history. Commercial population screening should be regulated by statute or by the Secretary of State until there is broad agreement on its efficacy and acceptability. We are not persuaded that screening for genetic predisposition to disease is appropriate (3.4) or could be conducted in such a way as to prevent discrimination (3.5).

Research and the application of finance

The setting of NHS strategies where only approved treatments will be funded will also direct research towards certain areas. Funding will divert research. Funding will set priorities.

Crude equations which purport to show cash savings from abortion from the cost of caring for a Down's individual should be merited on moral and philosophical grounds. This is necessary to protect other disabled persons already born and the moral sensibilities of mothers-to-be and ultimately the value that society places on human life. The slide from humanitarian to utilitarian ethics is a threat to the sick and vulnerable in the last analysis.

It would further be a disincentive to research and treatment for presently incurable inherited diseases. In a plural society where conscience is respected, vulnerable people will be better protected and, even in biological terms, bioversitility preserved (6.2).

The psychological benefits to the able-bodied by educating them at an appropriate age with Down's and other disabled children is real. They have rightly been called "the gentle prophets" because of their friendliness and "one day at a time" outlook.

Research regulation

Germline gene therapy (6.6) is rightly prohibited by the proposed *European Bio-ethics Convention*, the reason given being the unknown risk at the present state of knowledge. This will change following animal work but human germline alteration would require in vitro fertilization. This Catholics see as an additional obstacle being incompatible with the proper dignity of procreation. Whilst at present there is no complete teaching on germline gene therapy in the Catholic Church, the authors do not think that a strictly therapeutic intervention in gametogenesis would be at variance with established Catholic teaching. Only a serious disease could justify such a decision on behalf of persons and generations unborn.

General

Research and treatment must be set within legal bounds and also a moral perspective which serves man in his God-given destiny.

We thank the committee for allowing us to contribute to their deliberations and the Catholic Bishop's Conference for passing on the invitation of the Select Committee.

References

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[2] "Genetic Information and Health Insurance" NIH/DOE. Working Group on Ethical, Legal and Social Implications of Human Genome research" NIH, Washington 1993.
[3] "Genetics, Economics and Ethics" (as above).
[4] Ibid.
[5] "Gene Mapping Using Law and Ethics as Guides" G Annas, G and I Elias, Oxford University Press, Oxford 1992.
[6] "The Genome Project and Gene Therapy" A Cole, J Duddington, J Williamson, I Jessiman, Catholic Medical Quarterly, Vol XCII No. 4, May 1992 24-29.

Further Memorandum from Janice Wood-Harper (HGC 149) (6 April 1995)

GERM LINE INTERVENTION: AN ETHICAL VIEW

Summary of position

Genetic alteration of the germ line may become feasible in the future but, as for any new medical procedure, feasibility alone can never dictate its ethical permissibility.

Early deliberation on anticipated ethical problems in deciding its moral defensibility should be paramount in advance of decisions to implement such technology.

There is a consensus of opinion at present that germ line intervention should not be contemplated.

This is based largely upon uncertainties as to its possible misuse and/or the risks of disastrous irreversible changes to the genetic constitution of future generations. Such reservations are intensified by the knowledge that future generations cannot consent to alteration of their genetic inheritance and can therefore have no control or freedom of choice over any modifications which are made. Thus their right to autonomy is violated and also any right which may exist to inherit a genotype which has not been artificially tampered with.

The right of autonomy, however, is not absolute and may be superseded by the right not to be harmed by inheriting, for example, a preventable genetic disorder which predisposes to a serious and incurable disease.

Other main ethical concerns which can be anticipated:

(i) Problems in making decisions as to the type of interventions which will be permitted and the choice of subjects for genetic alteration.

(ii) Restriction of individual freedom in life decisions, such as reproductive choices, for genetically altered subjects.

(iii) Equitable access to treatment and justice between individuals and nations.

(iv) Dangers of the "slippery slope" into enhancement engineering and eugenics.

(v) Adverse consequences of changing the human gene pool.

(vi) Permissibility of "playing God"?

Germ line interventions should not be totally prohibited on the basis of unjustified fears.

Decisions should only be reached after:

(i) Deliberation as to the efficacy of the procedure after extensive research.

(ii) Assessment of the balance between potential benefits and risks.

(iii) Consideration of ethical issues which might arise; and.

(iv) Formulation of protective policies to safeguard against possible misuse of the knowledge and technology.

As techniques of genetic engineering become more advanced so possibilities of applying them to manipulation of the germ line will be increasingly debated. Although medical research using human subjects is strictly regulated, the possibility of adverse consequences of the clinical application of scientific knowledge can never be totally eliminated. Fears about potential dangers do not by themselves, however, provide sufficient justification to prohibit implementation of revolutionary medical procedures and thereby deprive society of the potential benefits.

New genetic possibilities, such as germ line intervention, call for an extension of traditional views of morality beyond the short-term consequences of present actions.

It becomes necessary to consider the long-term effects of the application of such technology in relation to not only the potential for benefit or harm to the physical health of future generations but also to the possible violation of their rights and ultimately to the prosperity of the human race.

Respect for future generations and the opinions which they might hold must be a predominant concern in any debate on the moral permissibility of such a revolutionary medical procedure which will directly affect both.

Discussion of the position

Arguments in favour of permitting germ line interventions

Germ line interventions may provide the only effective means of correcting certain defective genes such as those which cause multi-organ disorders. It should not, therefore, be dismissed as a form of beneficial therapy solely on the grounds of current insufficiency of knowledge and research, specifically in relation to the stability of engineered genes over several generations, the potential severity of the consequences of any errors or unanticipated, deleterious side-effects.

Possible benefits to be gained from germ line therapy over any existing forms of therapy:

(i) The alleviation of human suffering and death from diseases for which there are currently no effective alternative therapies or known cures;

(ii) The ultimate elimination of major diseases;

(iii) Overall economic advantages for society.

The technique could constitute a one-time treatment.

If implemented on a mass scale, it might conceivably bring about the total eradication of selected major diseases.

Anticipated problems in permitting germ line interventions

"Germ line gene therapy" presents a fundamentally different and potentially more dangerous option than "somatic cell gene therapy".

By inserting engineered genes into the germ cells, it alters not only the treated individual's genotype but also the genetic constitution of subsequent generations. The consequences of this difference are crucial to the debate as to whether it is ethically permissible to transgress the divide between research on germ line therapy and its implementation into clinical practice.

Difficulties are envisaged in defining the diving line between germ line interventions performed for therapeutic purposes and those which would be classified as enhancement engineering.

The aim of the latter is to produce a desirable trait by selectively altering the genome to augment an existing characteristic.

The distinction could be significant in deciding the permissibility of any particular intervention.

Examination of the validity of reasons forwarded to justify manipulation of the germ line is necessary before its clinical implementation.

(i) Although it could be upheld as producing a moral good in preventing disease, it can also be argued that a similar end may be achieved by means which carry lesser risks of harm, e.g., somatic cell gene therapy or prenatal diagnosis and selective abortion.

(ii) The efficacy of any proposed genetic alteration of the germ line should also be considered i.e., how likely is it that an anticipated beneficial outcome will be achieved.

(iii) Predicted economic advantages, that is the one time cost of the procedure, need to be weighed against the cost of repeated hospitalisation, therapies, drugs etc. in successive generations. Despite probable high initial investment in technology and training, it might prove to be a more cost-effective use of scarce medical resources in the longer term.

Consideration of the ethical implications of germ line interventions

Assuming that real benefits can be demonstrated, it then becomes imperative to speculate upon the ethical implications of germ line interventions.

Harm could result not only to the physical health of present and future generations but as a consequence of the procedure itself or its implementation being contrary to basic ethical principles. Thus the moral defensibility of any proposed intervention must be examined.

Ethical concerns relating to germ line interventions addressed

Problems in decision making

Complexities may be contemplated in decisions on issues such as the provision of services; the selection of individuals for treatment; and types of interventions which are to be permitted.

(i) *Provision of services*

Would the government (NHS) provide funding or, as would be more likely, would services be available only to those who could afford to pay through the private sector.

Access to services would, at least initially, be limited. Who would decide how resources were allocated and how would such decisions be justified?

(ii) *What type of interventions would be permitted and who will benefit?*

Who will contribute to decisions as to which genes are to be altered or corrected and the selection of individuals to be treated—geneticists, the medical profession, politicians, ethicists, the public?

On what basis will such decisions be made—severity of disease symptoms caused by the genetic disorder; effectiveness of current therapies; frequency of the disease in the population; cost to society of medical care, treatment etc? Would a serious, incurable disease which was rare in the population

be given lower priority than a less serious disease with no effective therapy but which affected a larger proportion of the population?

Will paying individuals be able to dictate what sort of interventions are performed on their embryos?

Can some forms of enhancement engineering be ethically justified? What sort of enhancements might be permitted and who should decide on where the dividing line is to be drawn?

What sort of regulation of practice will be necessary?

Issues concerning consent to genetic selection of the next generation

(i) The embryo can neither participate in decision-making nor consent to any intervention which would permanently alter its genotype.

(ii) There are opposing views on the moral rights of the embryo and the extent to which the embryo should be protected in order to preserve any such rights which it might possess.

(iii) The possibility of unforeseen, deleterious repercussions of germ line interventions would, for some time, determine the safety limits of and extent of overall benefits to be gained from the procedure. Consequently, any decision to alter the genetic constitution of an embryo, even assuming that such a decision is made with the intention of safeguarding the best interests of the person it will become and that person's descendants, must at minimum be given careful consideration and should be subject to strict controls.

(iv) It is likely that the consent issue would be viewed differently depending upon the kind of intervention which is considered. For example, genetic alteration to remove the risk of life-threatening disease might be considered to be more justified as a morally responsible action to prevent a more serious harm, even when balanced against the risk of possible adverse side effects (most traditional medical interventions involve some element of risk), than an intervention aimed at enhancing desirable traits, selected by parents, in future children.

Risk of discrimination

(i) Third party interest in information about individual genomes is likely to increase in the future. The potential exists for such information being used as a basis for discriminatory practices.

(ii) Insurers and employers might positively discriminate in favour of individuals who have been genetically altered to eliminate the risk of disease or to enhance a desirable characteristic, such as intelligence. Similar discrimination might then be applied to children who had inherited the same altered genes.

(iii) Such a situation would raise the problem of injustice for those individuals whose genes had not been altered, as a result of factors, such as lack of finance or access to services, which are beyond their control.

Restrictions on individual liberty in life decisions such as reproductive choices

(i) Individuals might eventually be allocated, by various institutions, a social role in life based on their genetic constitution.

Thus limitations might be imposed upon the autonomous decisions of genetically engineered individuals.

(ii) In order for the advantages of genetic modification to the germ line to be perpetuated in future generations, it would become necessary to ensure that the modified genes were transmitted effectively by restricting choice of reproductive partners to similarly altered individuals. This might even be enforced by government to protect financial investment in provision of services.

(iii) As more types of genetic alteration became commonplace, so individual freedom in the choice of a genetically compatible partner would become even more limited and prone to complexities such that "mating agencies" holding comprehensive details of personal genetic profiles may become necessary, raising additional problems associated with confidentiality and access to genetic data.

(iv) Initially inbreeding amongst an elitist group could be expected to lead to an increase in incidence of a variety of other genetic conditions and so negate some of the benefits previously accrued.

Inequities in access to treatment

(i) Problems can be anticipated in the just and equitable allocation of limited services for germ line intervention in view of the unlikelihood of any general provision of treatment.

(ii) As it would be impossible to provide equal opportunity for treatment to all those who could potentially stand to benefit and on whose behalf decisions had been made in favour of germ line intervention, the situation would require that some sort of selection procedure be used.

(iii) In practice, due to high initial costs of technology and professional expertise, it is probable that such interventions would predominantly be available to those who could afford to pay, rather than on the basis of prioritisation of health needs.

(iv) The potential for injustice in relation to the allocation of genetic treatment and its consequences can be considered on both an individual and international basis.

Justice between individuals

(i) It is unlikely that germ line interventions could be provided to all individuals who would stand to benefit on a just basis.

(ii) Consequently this situation would promote inequalities by creating a privileged class of genetically altered individuals.

(iii) In addition to health benefits, the social advantages to be gained by such people could be immense.

(iv) The potential for unfair discrimination based on genetic status emphasises the importance for allocation of treatment to be seen to be based on ethically sound grounds of medical need, rather than on personal wishes, ability to pay or comparative social worth.

(v) If some forms of enhancement were permitted, then such genetically altered individuals might well be victims of discrimination by a society which responded negatively to those who made use of the new technology for their own "betterment" rather than for the alleviation of disease.

Justice between nations

(i) Justice would require international co-operation to ensure that all nations are given equal opportunity to benefit from the new technology.

(ii) It is inevitable, however, that those nations which have made the largest investments in technology and expertise for human genome research will expect to be amongst the first to benefit from the new medical procedures, in terms of improved health and financial return. Support for this viewpoint is provided by issues which have already arisen concerning "ownership" of genetic data and the "right" to dictate how it is used, compounded by intensely competitive commercial interests within the international biotechnology industry and the struggle between the superpowers for political and economic dominance.

(iii) The probable inequity of access to treatment would be most marked between developed and developing nations and, in the latter, would constitute a further source of injustice to already underprivileged and vulnerable populations.

(iv) Inequality between individuals and nations would be an unavoidable consequence of the implementation of germ line interventions.

(v) Although justice may be viewed as a moral ideal for which to aim, in the context of access to medical treatment it is almost impossible to achieve.

Current medical services, particularly on a global scale, are seldom perceived as being allocated on a just basis, but yet other overriding moral considerations provide justification for their practice.

Dangers of the "slippery slope" into enhancement engineering and eugenics

(i) Genetic interventions have the potential to be eugenic, that is, to "improve" inborn traits to the ultimate advantage of the race.

(ii) Difficulties in deciding the moral acceptability of some interventions might be expected to arise when they fall within the indistinct demarcation between negative and positive eugenics.

(iii) A commonly expressed fear concerning germ line intervention is that, were the practice to be ethically sanctioned, then the temptation to push the boundary beyond the limits of moral acceptability would be inevitable, leading to a "slippery slope" into enhancement engineering.

However, it can be argued that such fears of technology being misused do not justify denying society the benefit of reducing the burden of serious diseases. Rather they emphasise the need for limits to be set according to medical and ethical criteria and for controls to ensure that these are adhered to.

(iv) The potential for eugenics is not a new phenomenon arising exclusively from genetic research and technological advances. Historically its realisation has been curbed by social and political controls and there is reason to believe that these will continue to be effective in the future.

Adverse consequences of changing the human gene pool

(i) Germ line intervention might change the human gene pool and produce deleterious effects on the delicate balance of nature.

(ii) It is argued that we have no right to decide which genetic traits should be introduced and which eliminated from the gene pool and thereby to effect intentional alterations to the fundamental nature of our existence or inherent "humanness".

(iii) Unless germ line intervention was implemented on a mass scale, it is unlikely that significant changes would result to the human gene pool.

(iv) If the practice became more commonplace, permanent changes could reduce the genetic variability on which evolution is dependent.

It is doubtful, however, whether this alone could justify its prohibition since this consequence would arguably be no different from the indirect effects of exercising a choice of mating partner; genetic counselling; or pre-natal screening; which are generally considered to be morally acceptable.

(v) Another major concern is that irreversible, undesired changes to the gene pool will result from ignorance or design.

However, other ethically defensible medical therapies such as radiotherapy which can produce genetic damage; or those which successfully treat genetic diseases such as diabetes, haemophilia or immune deficiency and thus preserve deleterious genes that would otherwise be deleted, also indirectly contaminate the gene pool.

(vi) In support of germ line intervention is the view that, by artificially selecting only "beneficial" genes to be inherited by future generations, it would function to improve evolutionary prospects.

The permissibility of "playing god"?

(i) *In support of the view that germ line interventions should be prohibited on the grounds that they would constitute "playing God":*

— Germ line invention would interfere with the identity of the species and the natural process of evolution.

— The religious view is that we are made in the image of God and therefore that the germ line should remain sacrosanct.

— If individuality is deemed to be determined by the inheritance of a unique genotype, then germ line interventions might be construed as orchestrating the creation of a new individual.

— These objections centre on the concept that we should allow "natural" mixing of genes and have no right to intervene and alter the course of nature.

(ii) *The argument against this view*

— All types of medical interventions could be criticised on the grounds of interfering with the course of nature and thus "playing God" and yet the permissibility of the majority is generally accepted.

— "Natural" processes have allowed serious adverse genetic traits to develop and affected individuals to suffer severe symptoms and premature death. If the technology exists which can benefit such individuals and their decendents, then there is a strong moral obligation to use it. It may, in fact, be considered unethical to prevent its implementation.

— Many diseases and associated suffering have resulted, not necessarily from "natural" influences, but from human interference with the environment and choices about lifestyle.

— Humans have, through natural evolution, acquired the mental skills necessary to increase their scientific knowledge and develop technology to reverse past "mistakes" and "improve" the species.

— It is conceivable that we will need to effect rapid inheritable alterations to our genotypes for protection against increasingly hostile surroundings. Artificial acceleration of the evolutionary process, and even forms of enhancement engineering which currently may seem "frivolous" or morally indefensible, might be justified to ensure the survival of the species.

Summary

(i) The complex and unique ethical issues involved in germ line intervention necessitate that decisions as to its moral permissibility be made after timely deliberation before its inception based on the implications not only for the embryos which are corrected and the people they will become but also for future generations.

(ii) The possible benefits to be gained by individuals and humanity must be weighed against the probable sacrifice of justice and any risk of harm.

(iii) If, finally, it is accepted as ethical, then stringent controls over its implementation should be formulated to minimise risks arising from either a lack of knowledge or its misuse.

(For details and bibliography see: Wood-Harper, J: "Manipulation of the germline: towards elimination of major infectious diseases?" in A Dyson and J Harris (eds): *Ethics and biotechnology* (Routledge, London, 1994)).

Memorandum from the Joint Ethico-Medical Committee of The Catholic Union of Great Britain and the Guild of Catholic Doctors (HGC 150) (April 1995)

The Joint Ethico-Medical Committee is composed of members drawn from the two parent bodies, the Catholic Union of Great Britain and the Guild of Catholic Doctors.

The Catholic Union is an organisation of the Catholic Laity which is not affiliated to the hierarchy and which represents the Catholic viewpoint, where relevant, in Parliamentary and legislative matters. The Guild of Catholic Doctors represents Catholic Medical Practitioners of the United Kingdom.

The following response follows the format of the "Questions" raised by the Committee in the Appendix to their Press Notice dated 3 November 1994.

General ethical and regulatory

1.1 Until we know more about genes we are not well able to make decisions about regulation of genetic material. There seems every reason to believe that such information will, eventually, be forthcoming. However, we may be able to say from certain basic principles (respect for human life, the institution of marriage, etc.) that some aims and some methods or forms of research ought not to be permitted. Much of this is encapsulated in the Helsinki Declaration.

1.2 We are unable to comment in any detail on the policies of the MRC and research funding bodies, but it is not clear whether their policies do have sufficient regard to the ethical and social consequences of human research.

1.3 We do not believe that society could declare certain research topics to be prohibited because they are likely to lead to insuperable problems, but—as above—society would be entitled to say that certain aims and routes of investigation are wrong in themselves and should not be employed (e.g., the creation of human embryos for destructive methods of analysis). In other words there are no grounds for saying good may not be done in case evil might follow from it (unless the whole aim in itself were evil): on the other hand evil may never be done even if good may come of it. Investigation should lead to the remedying or treatment of disease, not to the eradication of potential sufferers. Geneticists should, however be aware of wider fields than their immediate research goals and should be involved in debate about the desirability or otherwise of the consequences. It is possible that geneticists are pursuing hidden agenda which they do not publicise for fear of being stopped.

1.4 Human genetic research may lead some to a more deterministic point of view, but this is not necessarily the case. "If something can be done someone will try to do it!" Society has to decide on the desirability of genetic interventions, and it would seem to be the general opinion that—even for somatic cell therapy—such intervention should only be undertaken for the alleviation of genuine handicap or disease.

1.5 Some consider germ line intervention always to be wrong because, in the nature of things, we cannot obtain the consent of future generations who will be irrevocably affected by our actions—possibly in ways we cannot foretell—and to which their approval is by no means a foregone conclusion. It should certainly be prohibited at the present time. We are not clear what might be meant by "playing God" though it presumably refers to action on our part which will have unforeseeable and uncontrollable consequences for others [in the future]. The proposed UN declaration should make it plain that the human genome is something given—by God, or at least by nature—which can be discovered or explored, not invented, and cannot be subjected to rights of ownership or patenting.

Public awareness and education

2.1 Public knowledge of the subject is, by and large, minimal. It is difficult to find enough people who feel at home with the basic science even to monitor what is going on. Steps to improve this are desirable, presumably by well balanced and impartial TV, videos, lectures, books and articles, etc.

2.2 Little anxiety is expressed until particular instances are brought to the public notice by the media, and then it is difficult to obtain a sensible response. For example there was much opposition to the genetic engineering of tomatoes (probably relatively harmless) but little concern about the use of bovine somatotrophin injections to improve the milk yield in cattle which—by entering the milk—can affect the food chain and possibly cause serious harm to children. Improved knowledge would lead to better informed debate and assessment, and less "knee jerk" suspicion.

2.3 Unfortunately the media are liable to excite unreasonable hopes—one of the rare instances where "good news" sells?—whereas genuine knowledge and understanding would help to temper this.

2.4 There is a possibility that genetics could be seen as "determining" and thus "excusing" socially unacceptable behaviour. As almost all traits are multifactorial such information could only be part of the explanation at best. The remedy would seem to be appropriate education of the judiciary! We hope genetics would not be used to justify reductions in care programs as suggested.

2.5 Christians believe in free will, not determinism, and we would regard genetic explanations as providing a very inadequate explanation of human behaviour. The right question would have to be "what influence, if any, does genetics seem to have in the fields of human behaviour, ethics and belief?" or, in the case of crime, "what mitigation, if any, can genetics offer for this behaviour?"

Genetic disease

3.1 We do not have figures for the division of genetic screening between routine and research. We cannot sufficiently emphasise the absolute necessity for proper counselling of expectant mothers and their fully informed consent before any screening is done: some evidence suggests that this is not always being carried out. It is, of

course, to be deplored that the result of antenatal screening—if an abnormality is found—is usually termination of pregnancy rather than any attempt to alleviate the disease. Some disease with a known genetic cause may be missed since most screening is only triggered when there have been abnormalities in a previous pregnancy or where a preliminary test has appeared abnormal.

3.2 We are not aware of any significant ethical differences between somatic cell gene therapy and other forms of transplantation procedure.

3.3 We believe that an individual's genome should be regarded as confidential to that person and only with his or her consent revealed to others. Insurance companies should have the same right to require an individual to undergo genetic testing before being granted life insurance as is the case for any other disease, since their actuarial assessment needs to be based (for the benefit of all their clients) on known predisposition to disease. In this case, however, the results should also be made available to the client through their own doctor, with appropriate counselling, such as currently done with HIV tests for insurance. We do not, however, consider that an employer has any right to demand or require genetic information, except on a voluntary basis where the conditions of the job are known to be harmful to the health of certain genetic groups. In all this we have seen a parallel with the current situation where insurance companies may require certain tests prior to life insurance, especially for larger sums, but employers have no right to demand medical evidence prior to employment (except for purposes of an occupational pension scheme).

3.4 Population screening for genetic disease would seem appropriate and justifiable only where there is a reasonable chance of an effective remedy for the condition in question. If it is undertaken then counselling is essential before any tests are undertaken. We have no views about organisation but believe that regulation should include the approval of a local (or national) ethics committee.

3.5 If screening were to become general then the knowledge of the genotype should remain confidential to the subject themselves and they should be protected from any other way of discrimination on genetic grounds.

3.6 If the possible genetic disorder were a serious one then people would be well advised to seek genetic information from would-be partners. There should be no compulsion. We understand that it is widespread practice in certain mediterranean countries to test for thalassaemia and other haemoglobinopathies before intended marriage and that this is well taken up by the public. We could envisage a similar willingness to take up such screening in this country for cystic fibrosis, but we would oppose any suggestion that pre-marital screening should be obligatory, whatever the disease. Screening in minors would only be acceptable if they were to benefit from the outcome by way of effective treatment or at least modification of life style.[1] Future research, of course, may make screening easier, safer, and more available. Economic factors should not be allowed to override ethical and medical considerations.

Economic benefits

4.1 Knowledge of genes might be expected to make accurately targetted treatment, either by gene therapy or by drugs, more readily available.

4.2 At the present stage gene therapy remains more difficult, more costly and less certain than most conventional methods. It is likely that it will always be more expensive.

4.3 Patent protection causes us considerable concern. We consider that naturally occuring genes and the genome as a whole are "given" and can be discovered, but are not being invented, and should on no account be patentable. Techniques used in the discovery or in the application of discoveries to further study or treatment could, as inventions, be patentable. The position of newly constructed genes or gene sequences is more difficult, and we can understand the desire of individual firms or institutions to protect their (very costly) work. On the other hand we do not think that any organisation or company should have the right to hold the whole human race, or even particular genetic parts of it, to ransom. If it were decided to allow *invented* (as opposed to discovered) gene sequences or genetic techniques to be patentable we suggest that such patents should only last for a limited period of years—such as is currently the case with new drugs.

4.4 We do not have the facts about genetic based industry in the UK but there can be no doubt in general that more developed countries will require more stringent (and expensive) safeguards for the protection of their populations than would third world countries. This, of course, increases costs and encourages unscrupulous operators to exploit their opportunities in the third world with increased risk to those populations and, indeed, to the world as a whole. Funding is a separate problem and it is our understanding that we may lose research to other developed countries because of lack of necessary finance.

Research

5.1 The advantages of mapping the whole human genome are not clear, and indeed will only be fully known when it has been done. The project will add to the common fund of knowledge, and may eventually reveal the

significance of the so-called silent areas, and perhaps that they have a function. In the meantime it would be less costly only to analyse expressed genes.

5.2 It remains to be seen what we will learn from the project and,

5.3 In particular, to what extent the genome determines human characteristics, or the environment affects the expression of genes.

5.4 The understanding of organisations and coding of the genome is in the early stages but is progressing rapidly. There is no doubt that gene therapy (but most especially germ line therapy) *will have* unforeseen effects as well as those that are intented.

5.5 Financial support world wide may be adequate, but we believe that without more central support this country is in danger of being left out or left behind.

EVOLUTION

6.1 While we believe evolutionary theory to be broadly correct we know of no evidence to show either that change is taking place at the present time, or in what way.

6.2 Some evolved characteristics (such as sickle cell trait or fibrocystic disease) which have beneficial effects in undeveloped societies or different environments have not only become redundant but actually harmful in our present situation.

6.3 It is impossible to say what further effects environmental changes may have or

6.4 To what extent the pursuit of scientific knowledge might affect evolution.

6.5 It has been shown that the effect of selective termination is much less than at first sight might be expected, since the killing of subjects of such diseases does little if anything to reduce the abnormal gene pool (i.e., if you kill all the males with haemophilia the number of female carriers is correspondingly increased).[2,3] Selective fertilisation might be expected to have a greater effect, but only a very small proportion of pregnancies could be managed this way.

6.6 Deliberate manipulation of the germ line is likely to introduce much greater changes than the average mutation, and be more liable to be disruptive.

6.7 We consider that human sexual reproduction should be a matter of free choice for the individual, and that clinical (or legal) interventions should only be by the individual's free choice.

References

[1] Grigg L. Knowledge of risk allows adaptation. *BMJ* 1995; 310: 859

[2] Motulsky A G, Fraser G R, and Felsenstein J. Public health and long-term genetic implications of intrauterine diagnosis and selective abortion. *Birth Defects: Original Article Series* 1971; VII, No. 5: 22-23.

[3] Boss J A. How voluntary prenatal diagnosis and selective abortion increase the abnormal human gene pool. *Birth* June 1990; 17(2): 75-9.

Memorandum from Dame Joan Slack (HGC 152) (12 April 1995)

Thank you for inviting me to comment on some of the questions on human genetics. It was very helpful to see the questions addressed in the press release and the transcript of the 22 March meeting. I have commented separately on both. Sir Gerald was interested in the implications of genetic information for insurance and I have commented on this separately.

I write as a retired clinical geneticist with experience in setting up and running General Genetic Counselling Clinics and Family Cancer Clinics: for Colorectal Cancer at St Marks Hospital and for other Hereditary Cancers at the Royal Free Hospital. My main research interests have been in Family Risks of Coronary Heart Disease and of the common cancers (mainly Colon, Breast and Ovary), and in screening for Down's Syndrome in the Antenatal Clinics.

Perhaps my most relevant publications are:

BNJ 1990 *101* 336-368 Colon Cancer.

JM Genet 1992 *29* 154-157 Breast Cancer.

Soc Sci Med 1987 *9* 725-731 Down's Syndrome.

GENETIC PREDISPOSITION AND INSURANCE

Insurance against disability or death is a long standing association between health and the market forces. As I understand it, financial success in insurance depends upon attracting as many people as possible to take out policies which are costed according to risk on an actuarial basis. The greater the number of policies, the more accurate the risk calculation will be. The more restrictive the policies the fewer people will take them up.

Insurance is a matter of trust between insurer and the policy holder and cheating by policy holders has always been part of the risk involved. Questions about medical conditions are frequently, though not always, asked by insurers who can either accept the risk, refuse the policy, weight the policy, ask for medical examinations or request verification of statements from family doctors. I do not see any difference between genetic disorders, known or unknown and the present position. Genetic disorders are usually clearly revealed on death certificates and insurers have a right to refuse payment if cheating has occurred, just as they do now.

At present this seems to be no problem in an insurance company asking for a family history and weighting can be based on the simple genetic screening test. If a disorder is known to the client, genetic or otherwise, it should be declared just as a previous operation for breast cancer or angina pectoris must be declared; as for other declarations this has to be a matter of trust. Polymorphisms (natural variations) associated with risk of common disease are very common and predict only a small proposition of risk, so that it seems unlikely that insurance companies would gain from excluding a large number of clients for a small increase in risk of late onset disease, such as Alzheimer's disease. By comparison single gene determined diseases such as Huntington's chorea are individually very rare.

HUMAN GENETICS QUESTIONS FROM PRESS NOTICE

1. *General Ethical and Regulatory*

1.1 In order to make clinical use of "The way genes work" we need to know the implications and options available to a relative with an affected family member. We need to know:

(1) The mode of inheritance.

(2) The penetrance of the mutant gene over a life time at different ages.

(3) The availability of diagnostic tests.

(4) Empiric risks to relatives if diagnostic tests are not available.

(5) The burden of the disorder and its variability.

(6) Whether treatment is available.

(7) The options for prevention.

Examples:

1. Cystic Fibrosis—recessively inherited.

Risk one in four after birth of affected offspring.

Frequency one in 1,600 live births. One in 20 Carriers.

Penetrance: sometimes neonatal onset, usually early childhood occasional delay to early adult life.

Fully penetrant over life time.

Diagnosis available prenatally and for most carriers.

Burden severe.

2. Familial Hypercholesterolaemia. Dominantly inherited. Carrier of single mutant gene. Frequency one in 250.

Expressed as hypercholesterolaemia from childhood.

Affected male 50 per cent have coronary by 50, 20 per cent dead.

Affected females 25 per cent have coronary by 50, death rare.

Diagnostic tests are available.

Burden negligible until diagnosis.

Severe after coronary heart disease.

Treatment available but benefit doubtful.

3. Breast Cancer—multifactorial. Four per cent dominantly inherited.

Frequency of single dominant gene one in 3,000 women.

Most frequent in patients with early onset.

Penetrance 80 per cent in gene carriers.

Genetic markers available.

Risk to relatives diminishes with increasing age and with increasing age of onset in affected relatives.

Optimum screening protocol has not been established.

Options mammography, ultrasound or mastectomy.

1.3 Society has an obligation to monitor the direction of research topics with a view to anticipating insuperable moral problems. Geneticists undoubtedly should and do think widely about the consequences and possible applications of their research—in this they are monitored and advised by local ethical committees. Clinical geneticists are constantly in touch with the public over the application and need for research. In the past genetic counselling clinics have been open to self referrals which has increased their sensitivity to public demand but his has stopped since the introduction of purchaser/provider organisation.

The most worrying aspect of genetic research is the failure of departments to share results (positive and negative) with colleagues at home and abroad because of the tight competition for funds and reputation between departments and universities. This is undoubtedly delaying development and dissemination of knowledge.

An Advisory Body for genetic research such as the Gene Therapy Committee might be helpful for discussion. Legislation does not seem appropriate in such a rapidly changing field.

2. *Public Awareness and Education*

2.3 I have not met unreasonable expectations of the benefits that might come from genetics in the genetic counselling situation. Patients come to these clinics often in considerable anxiety about their risks. They are usually relieved when they know and understand the risks and make very sensible decisions about the options available, choosing those which will suit their individual needs. Usually those who come to genetic clinics are themselves well and have time to wait and hope for developments. In my experience they have been well informed and there has been time for discussion.

2.4 It would not be justifiable to reduce social programmes of health education and welfare because of a potential reduction in the number of genetic disorders through prevention. Genetic options for prevention cannot be made compulsory, their acceptability varies between different individuals and different races and religious creeds. Genetic options are therefore not available to all and a significant proposition of disability will arise from unpredictable congenital malformations[1] and fresh mutations. If the number of genetic disabilities are reduced the quality of welfare and education should be improved and only when this has reached an optimum level and numbers have been shown to be reduced should adjustments in social programmes be made—not on the grounds that numbers should or could be reduced by genetic methods. The costs of genetic screening programmes all amply repaid.

See ref. Soc. Sci. Med 1987 *9* 725-731

A problem arises because the provision of funds for prevention comes from finance for health and the benefits accrue to finances for education and social welfare.

3. *Genetic Disease*

3.1 The first indication of genetic disorders is usually through a simple family tree by the general practitioner or an examination of the newborn by the obstetric/neonatal paediatric team on examination of the new born.

[1] For example: Down's Syndrome contributes 30 per cent of the severely mentally handicapped. Screening for Down's Syndrome is available prenatally and might realistically pick up 50–60 per cent. of affected foetuses with a possible reduction of 15 per cent of severely mentally handicapped. Not all will be defected and not all parents will opt for screening and not all will wish to terminate an affected foetus. The options must remain and facilities for care will continue to be needed.

The child development team may pick up early development delay but it is usually the family who recognise the likelihood of genetic disorders, particularly those of adult onset. There is often delay and some difficulty in persuading the primary health care team that there is a need for genetic advice because GPs and practice nurses, who often take the family tree, are not well informed about genetic disease and the many variations in presentation. For example: The likelihood of a genetic predisposition of common cancers which present unusually early.

There is a measure of ignorance in the medical profession about the genetics of common disorders which, combined with reluctance to spend money on the apparently well, mitigates against the recognition and referral of patients with genetic disorders.

At present it takes about 10 years from writing the results of a research programme to the general clinical use of the findings. The use of research findings is often enforced by the legal proceedings of negligence because well established research knowledge has not been used.

For example: Compensation for failure to offer screening for Down's Syndrome to a woman of 40 years pushed the screening programme forward in NE Thames as no other scientific argument had managed to do.

In Holland I believe research is published, then applied and monitored carefully in a limited number of centres before becoming routinely accepted for general clinical use. The progress from research results to clinical use in the UK at present is haphazard.

3.2 I see no ethical questions about somatic cell gene therapy which are different from other types of therapy.

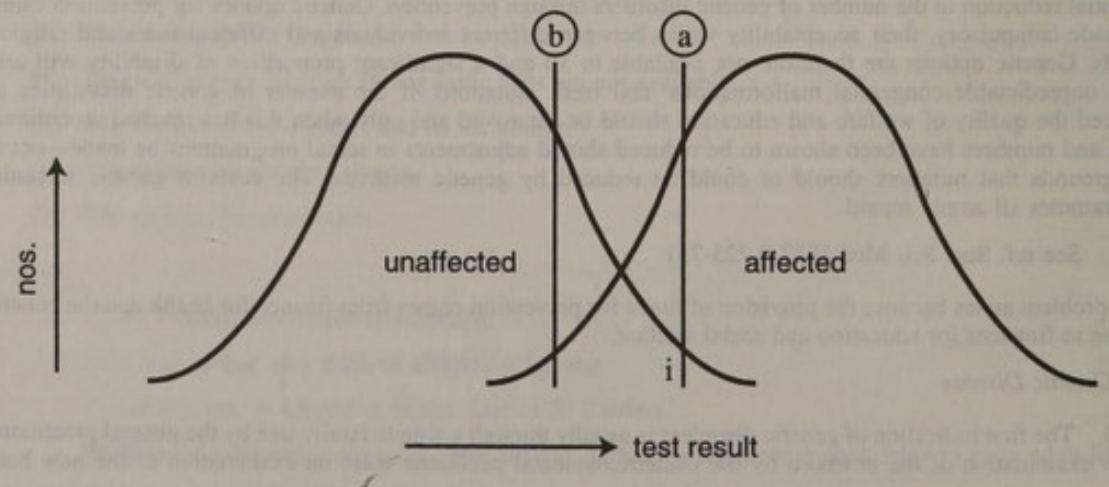
3.3 This question answered on separate sheet re insurance.

3.4 Population screening for genetic disease is appropriate when a screening test which is cheap and simple to perform accurately becomes available for a disorder for which early detection is likely to provide benefit. A screening test is usually not diagnostic but identifies a sub-group whose risks are higher than that of the general population and in whom more costly and perhaps invasive diagnostic tests have an increased likelihood of a positive result.

When a screening test is available it should be optional and information about the condition to be screened, including the burden and possibilities of treatment, the accuracy of the test and the way it will be reported as well as the implications of detection must be provided before the test is performed. No guilt or blame must be laid upon anyone refusing the test.

Simple screening tests are a family history (e.g., muscular dystrophy, coronary heart disease), age of pregnant mothers (e.g., Down's syndrome), recognition of ethnic susceptibility (e.g., Tay Sach's disease, Sickle cell disease). Some screening tests provide information of measurable risk at which further diagnostic tests should be offered.

For example: A cut off point (a) can be arbitrarily selected to provide a low false positive rate with a high false negative rate or (b) can be selected providing a high false positive rate and a low false negative rate. (a) will be cheaper than (b) because less people will be selected for the diagnostic test but more affected people will be missed.



The cut off point is selected on the basis of the acceptability of the risks involved, the acceptability of the false positive and false negative results, the costs of the procedure and the burden of the condition.

Screening should be organised for large numbers where tests can be standardised and their accuracy checked regularly. The results of screening should be carefully collected, monitored and published regularly. Well informed counselling should be available and readily accessible to all who are screened.

Regulation of screening should be based on a selection of the *risks* above which benefit from diagnosis can be predicted and regulated by cost benefit analysis. The number of involved can be readily moderated by selection of higher or lower primary screening risks.

3.5 If screening for a wide range of generic predispositions became routine the normal rules for medical confidentiality would presumably apply and would be particularly important for untreatable conditions of adult onset. In the near future "blunderbuss" genetic screening seems unlikely because of the high cost of molecular techniques and the rarity of the individual disorders. By the time "blunderbuss" genetic screening is commonly undertaken there may be satisfactory treatment for many more genetic conditions, for example by somatic gene therapy and the risks of the condition may be considerably improved by screening and appropriate treatment.

3.6 I have come across arranged marriages within certain ethnic minority groups where genetic information is sought between families. Ignorance or non-disclosure of a genetic trait can lead to great misery and sometimes return of the bride in disgrace to her family.

If educational courses among school leavers enabled young couples to talk to each other about genetic traits they would be able to sort out some of their problems before conception. I do not believe many couples who are free to choose will reject a partner on genetic grounds but they will be prepared for genetic counselling and better able to choose their options together.

For example: Tay Sachs disease is well explained through Jewish youth clubs.

4. *Economic benefits*

4.1 Knowledge of the location, sequence and gene product of the normal and abnormal genes regulating genetic disorders is needed before pharmaceutical companies can devise methods of gene therapy. Common disorders will presumably be the most advantageous for marketing purposes but not necessarily the easiest to produce.

4.2 I see no difference in principle or practice between gene therapy and conventional therapy. The same safeguards for safety are necessary. The cost of manufacture of gene products may be low compared with the cost of research and development but if successful will open up treatment for a large number of hitherto untreatable genetic disorders.

6. *Evolution*

One example of the frequency of the malaria resistant haemoglobinopathies in populations exposed to malaria, for example in Africa and around the Mediterranean. This frequency is reduced in the races of African origin resident in North America.

6.5 The evolutionary impact of selective fertilisation or termination will be very small since the aim is to prevent the birth of very seriously disabled individuals whose biological fitness is likely to be seriously disadvantaged.

Termination of recessive disorders is applied to the affected homozygote leaving the gene pool in unaffected heterozygotes undisturbed.

6.6 Manipulation of the germ line in the clinic or laboratory is directed with intent towards a limited number of conditions. Natural variation is random and applies to the whole genome.

MEETING OF 22 MARCH 1995 (HC41–vii)

A BRIEF COMMENT ON SOME OF THE REPLIES

Q592. The discussions concerning the frequency of genetic disorders in the UK population seemed somewhat confusing and may have been misleading.

Cystic fibrosis is the commonest *recessive* gene in the Northern European populations. The condition occurs in one in 1,600 live births in the UK population and the carrier is one in 20. Carriers have no known disadvantage to their health but one in 400 random matings will be between two carriers who will then have a one in four chance of an affected child. Until the affected child is born there is not usually a recognisable family history, especially in the UK where families are small (*ref 599*).

Carrier frequency of the rarest recessive conditions are usually between one in 50 and one in 100, the latter producing a condition with a frequency of one in 10,000 live births, for example, phenylketonuria.

In discussing the frequency of β.Thalassaemia in the Cypriot community in the UK a simple screening test has already been applied to select the susceptible ethnic minority group so a frequency of one in 200, with a carrier frequency of one in seven cannot be compared with the UK frequency of genetic disease.

To place the frequency of some common genetic disorders in the UK population into proportion.

Frequency	
Cystic Fibrosis	1 in 1,600, carriers 1 in 20
Down's Syndrome	1 in 650 all pregnancies at term
	1 in 50 in mothers over 40 years
Familial Hypercholesterolaemia	1 in 250
Breast Cancer	1 in 12 female population
	1 in 300 dominantly inherited

In selected populations:	
β Thalassaemia in Cypriots	1 in 200
Tay Sachs disease in Ashkenazi Jews	1 in 3,600
Carrier frequency	1 in 30

Q606. Dr Jones asked whether screened people "have a right to know". If all screening was optional as suggested in reply 3.4 there should be no problem because by "opting in" patients would have signalled their "wish to know".

Q635. Reply to Dr Jones. See answer to 6.5 in Press Release Questions.[1]

QQ645 and 690. Genetic predisposition and insurance, see separate sheet.[2]

Memorandum from SmithKline Beecham (HGC 155) (20 April 1995)

SMITHKLINE BEECHAM POSITION PAPER ON HOUSE OF COMMONS SCIENCE AND TECHNOLOGY COMMITTEE ON PATENT PROTECTION FOR HUMAN GENETICS

1. IMPORTANCE OF PATENTS TO PHARMACEUTICAL INDUSTRY

It is now beyond question that effective patent protection is the life-blood of the pharmaceutical industry. Put another way, without effective patent protection on a potential pharmaceutical product, then the high probability is that the product will never be developed by any non-subsidised pharmaceutical company as a pharmaceutical. Why should this be so? There have been countless articles written on this subject but a simple example will make the point. In toto, the UK pharmaceutical majors Glaxo-Wellcome, SmithKline Beecham and Zeneca have a current annual pharmaceutical R&D spend in the order of £2 billion with the hope collectively of launching between four to six new pharmaceutical products per year.

In rough terms, this amounts to a total R&D spend for each new product launched of between £300 million and £500 million. Once an innovator company has invented, developed, launched and promoted the new product, it is faced with the need to recoup this substantial R&D investment. The same is not true for an imitator or generics company. The economic reality is that a free market position on expensively developed new pharmaceutical products will destroy the commercial viability of a research based pharmaceutical industry. The patent system provides research based industry with the economic lifeline enabling, for a *limited* period of time, the innovator company to prevent copy products and so recoup its substantial R&D investment.

The important point is that any erosion in patent protection for products of a particular type e.g., human genes, enzymes, proteins etc., will effectively preclude the commercial viability of development of such products as pharmaceutical. In view of such profound implications, considerable caution should be exercised when considering the exclusion from patentability of any subject matter or technology that could advance the frontiers of medical science such as DNA and genetic technology.

2. GENETIC SCIENCE—THE NEW FRONTIER IN MEDICAL RESEARCH

Most therapies available today for chronic illness (e.g., rheumatoid arthritis, osteoarthritis, cancer and congestive heart failure) offer only *symptomatic* relief. They do not get at the root cause of these serious diseases

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[1] See p. 45.
[2] See p. 42.

we do not understand what the root causes are. The advent of genetic medicine will transform this landscape considerably and promises to yield new clues and insights into diseases that only recently were viewed by most as intractable. As a result new therapies will undoubtedly emerge, providing industry can be encouraged to invest the necessary billions of pounds in research and development.

The genetic diseases with which the public are familiar are rare disorders but because of their relatively simple genetic nature they have been much easier to study (e.g., cystic fibroses, Huntington's Chorea). For the most part these diseases are caused by mutations in a single gene (monogenic) and these will be in the first line of research if industry is provided with the necessary patent incentive.

However, the recent and relentless advances in genomic technologies have now made possible the study of more complex diseases which are likely driven by several genes (i.e., polygenic) acting in concert with critical environmental factors. The most fascinating prospect is that several important diseases, (e.g., atherosclerosis, osteoporosis), never previously considered to have a genetic component, are in fact turning out to do so. The surge of excitement that has resulted from this revelation is what is driving much of the new research and optimism on human disease, and will lead to a better understanding of these diseases and thus improved (curative) treatments. It is however unfortunate that most of these advances have taken place in the USA where industry has received greater incentives including patent protection.

The diseases that are driven by a strong genetic component and will undoubtedly benefit from R&D in biotechnology are the following:

Neurosciences

Alzheimer's

Schizophrenia

Common migraine

Depression

Anxiety

Cardiopulmonary

Asthma

Atherosclerosis

Susceptibility to stroke

Inflammation and Tissue Repair

Type II diabetes/obesity

Osteoporosis

Cancer (most types)

Europe's opportunity to be in the vanguard of research in the above areas is undoubtedly in serious jeopardy if patent protection for the fruits of such research in Europe is denied. It is therefore important that continued uncertainty in this area, e.g., by way of a new negative European Directive or even discussion at national level threatening protection in this area is quickly and finally resolved.

3. Patents on genetic products—the current status of patent law in Europe

The starting point for any consideration on the patentability of genetic products is the application of the normal requirements for patentability. To do otherwise would require a change in the law, an exercise that should obviously not be undertaken lightly, especially in relation to potential pharmaceutical products (see 1 above). In particular since effectively it would single out genetic products from all other areas of technology such an exercise could only be justified if the arguments for were very compelling. It is submitted that there is no good reason, compelling or otherwise, why patent law should be applied differently in relation to genetic products than all other areas of technology.

The main patentability criteria in Europe are novelty, non-obviousness and industrial applicability (Art. 52(1) European Patent Convention—EPC, and Sect.1(1)(a), (b) and (c) UK Patents Act 1977—UKPA). The appropriate application of these criteria should ensure that valid patent protection is only available for really useful and meritorious inventions in genetic research and not available for those advances which do not meet

these stringent criteria. Accordingly, and this is often a point of confusion, acceptance that e.g., human genes are in principle patentable providing they meet the normal patentability requirements does *not* imply that all genes will necessarily be validly patented for clearly many genes will *not* meet the stringent patentability requirements.

It should be noted that in Europe, there is also an exclusion from patentability on the grounds that the exploitation of the invention the subject of the patent is contrary to public policy and morality (Art. 53(a) EPC and Sect. 1(3)(a) UKPA) and it has been suggested that this exclusion should be invoked to prevent the patenting of genetic products. There are several important points here that need to be addressed viz:

(a) The relevant provision refers to the *exploitation* of the invention (and *not* the attempt to obtain patent protection) which must be contrary to public morality if the provision is to apply.

(b) As a matter of practice, this provision is narrowly construed, rarely applied and then only in extreme cases. For example, the official "Guidelines for Examination in the European Patent Office" suggest that a fair test to apply is to consider whether the public in general (i.e., not only special interest groups) would regard the invention as so abhorrent that the grant of patent rights for it would be inconceivable. An example given in the Guidelines is the invention of a letter bomb. Whilst it is possible to conceive of types of genetic inventions which might fall into this category (e.g., a method of human genetic manipulation to ensure the sex, appearance, intelligence etc., of a human baby), in general it is difficult to argue that many of the inventions that flow from genetic research, e.g., in the field of medicine, could be regarded as immoral.

(c) Patents in Europe normally have a maximum duration of twenty years and to exclude an invention from patentability on moral grounds, the Patent office should be reasonably confident that not only does the invention under consideration offend the morality requirements today but also that this will continue to be the case for the full period of the patent i.e., potentially for the next twenty years. Clearly our views on morality are influenced by time and there are numerous examples of what was regarded as immoral previously no longer being so regarded e.g., abortion.

(d) Our views on morality are clearly linked to our religious views and just as the distribution of the major religions varies geographically throughout Europe so too our views on morality. A good example again is abortion, accepted as morally acceptable in some countries in Europe but certainly not everywhere. Any attempt to apply Europe-wide standards of morality to patent law must accordingly be done with extreme caution.

(e) If an act is regarded by society as being so abhorrent that is should be deterred, the most effective way of deterring it is to legislate directly to make that act illegal. Tampering with the patent law will not deter and on the contrary, to permit the act to be patentable will if anything actually serve to increase the deterrence, since if actually patented any unlicensed use would constitute patent infringement and so could be prevented before the Civil Courts.

In the result, the normal criteria for patentability under European patent law have dealt effectively with new areas of technology that have sprung up hitherto without the need for any special cases. No special case is justified in relation to genetic research and the current safeguards are perfectly adequate.

4. The Draft Directive on the Protection of Biotechnical Inventions

The original justification for the draft Directive, when it was initiated in 1988, was the growing recognition of the increasing importance of biotechnology to a broad range of European Industries and its dependence on the protection of biotechnological inventions in Europe. The draft Directive did not however set out to replace national laws in relation to the protection of biotechnological inventions, but rather to provide guidance on the public policy and morality exclusion that exists in the EPC and national laws of member European countries (see 3 above). It is on this latter area that much of the debate has been centred and indeed on which much of the attention of special interest groups opposed to patenting anything derived from living organisms has been focused. In the result, on its progress through the complex European "Codecision" legislative procedure, any benefit to the pharmaceutical industry of a Directive that might have confirmed in clear terms that existing standards of patent protection should apply to biotechnology and provided guidance on how the public policy and morality exclusion should be interpreted in practice was whittled away ultimately to the stage where, after the compromise reached before the Conciliation Committee and the conflicting interpretations taken by the Council and Parliament sides of the Committee, it had become ambiguous and/or unclear and generally less than helpful.

It was therefore with some concealed relief to the Pharmaceutical Industry that the Conciliation Committee compromise was finally rejected by the European Parliament.

At the heart of the industry's concern was the way in which the debate concerning the morality exclusion had developed. In an attempt to prevent the patenting of genetic technology special interest groups artificially distorted the clear language of Art. 53(a) of the EPC. As a result the debate drifted to a consideration of whether the *granting* of patent protection itself might be regarded as contrary to public policy and morality rather than

the *exploitation* of the invention as required by the clear language of Art. 53(a). If we confine ourselves to the correct and narrow interpretation of Art. 53(a), then the question of whether inventions relating to products derived from living organisms should be excluded from patentability no longer has relevance. In this connection it is untenable to argue that the exploitation of such inventions, *as a whole*, is necessarily immoral. Rather each case should be considered on its own merits and the pros of the invention to the benefit of mankind versus the cons based on any moral issues should be taken into account.

Unfortunately, any attempt to put forward a new Directive will suffer from the same drawback as before and indeed because of increasing pressure from special interest groups even greater distortion of the clear wording of Art. 53(a) EPC and its national counterparts is likely to be the result.

Under the circumstances, it is submitted that the Pharmaceutical Industry's interests and as a result, society's interest in enjoying the potential medical breakthroughs that the industry can provide, are both best served by maintaining the legal status quo and *not* supporting the pursuit of a new Directive.

Conclusion

By way of conclusion we deal with the questions specifically raised by the Select Committee on Science and Technology viz:

- *How necessary was (or is) it to have a Directive on patenting?* . . . At this particular time it is *not necessary* and indeed *could be harmful* to industry based on the course that the original draft Directive had taken.
- *Was the Directive as amended by the Conciliation Committee satisfactory?* . . . *No,* it had become ambiguous and unclear and less than helpful.
- *If the industry is of the view that a Directive in needed, would a Directive which excluded human DNA from patenting be acceptable?* . . . Industry is *not* of this view and even if it were, it could not support a Directive which excluded human DNA from patenting which otherwise met the existing requirements for patentability.
- *Would it be possible to allow patent protection for the processes involved in biotechnological inventions whilst forbidding the patenting of DNA?* . . . In principle it would be possible but only by change in the law. Such a change however lacks any logical, legal or technological basis and would not have the support of the pharmaceutical industry. In this latter connection, recall the point made in section 1. above that depriving a product from patent protection would as a natural consequence in all likelihood preclude that product from being developed and introduced as pharmaceutical.

As a final point, it is important to recognise that the continued debate as to whether genetic products should be patentable in Europe is in itself doing damage to pharmaceutical investment in Europe. As long as the debate continues the temptation will be to invest in biotechnology outside Europe e.g., in the USA where the legal environment is less under threat and more industry-friendly.

Memorandum from British Biotech Pharmaceuticals Limited (HGC 157) (24 April 1995)

Thank you for your letter of 23 March requesting additional views from industry on two points—the draft Directive on the Protection of Biotechnological Inventions and the possibility of process patents for DNA which exclude patent coverage of the DNA composition itself. I would like to thank the Committee for the opportunity to respond on these two important issues. Although I am writing on behalf of British Biotech, the position adopted by the BioIndustry Association is equivalent and the views expressed below reflect those of many emerging biotechnology companies in the United Kingdom.

1. The Draft Directive on the Protection of Biotechnological Inventions

(i) *How necessary was it or is it to have a directive on patenting?*

The overall need for a harmonising Directive on biotechnology patents is questionable. Back in 1988 when the Directive was first put forward there was a need to clarify the position on patenting reproducible biological material and the extension of patent rights over subsequent generations. However, since then the European Patent Office and other major patent offices around the world, as well as the courts in many countries, have developed generally satisfactory patent law and practice in the area of biological material. In addition, the Directive's gestation provided a focus for strong lobbying from a number of special interest groups. In particular, the Directive raised industry concerns over a number of areas:

(a) The extension of ethical and moral criteria into the patenting process, particularly with reference to gene therapy, animal models and parts of the human body.

(b) The ambiguity surrounding patenting genes which are isolated from the human body.

(c) The Farmer's privilege over transgenic farm-saved seed.

(d) Compulsory cross-licensing by transgenic plant patent holders to plant variety holders.

Given the ambiguities in interpretation, especially in the final version, it was questionable whether the Directive would have harmonised patent law since different Member States could interpret a) and b) above in different ways. Throughout this whole process the UK industry position has been that if the Directive was not satisfactory then it would be better to have no directive at all. The final draft was very much on the borderline.

Given the decision of the European Parliament to reject the Directive, it is highly unlikely that any new version would be an improvement over the draft which was rejected. Indeed, it is very likely that a new draft would represent a substantial erosion of the patent protection which is currently available under the European Patent Convention and, for this reason, we would be strongly opposed to any resurrection of the Directive.

There remain some gaps in terms of national patent law practice, but the degree to which this would have been cured by the defective Directive is highly questionable.

(ii) *Was the Directive, as amended by the Conciliation Committee, satisfactory?*

The final version of the Directive put before the European Parliament was unsatisfactory. The main problem area which the Conciliation Committee attempted to resolve concerned Amendment 3 (Recital 10 of the Common Position). Recital 10 of the Common text reads as follows:

> "Whereas, in the light of the general principle that the ownership of human beings is excluded, the human body or parts of the human body, for example a gene, protein or cell in the natural state in the human body, or isolated from it, including germ cells and products resulting directly from conception, must be excluded from patentability. However, an invention incorporating isolated parts of the human body should not be unpatentable merely because it uses material of human origin, it being understood that the parts of the human body from which such isolated parts are derived are excluded from patentability."

The final Conciliation text read as follows:

> "Whereas, in the light of the general principle that the ownership of human beings is excluded, the human body or parts of the human body as such, for example a gene, protein or cell in the natural state in the human body, including germ cells and products resulting directly from conception, must be excluded from patentability, *whereas, however, an invention including industrially applicable parts obtained by a technical process from the human body in such a way that they are no longer directly linked to a specific individual,* should not be unpatentable merely because of their human origin, *even when their structure is identical to a part of the human body,* it being understood that the parts of the human body from which such parts are derived are excluded from patentability."

The main problem with this text, which appears to have been drafted in the light of the Moore case in the United States, was that it was ambiguous: The phrase "in such a way that they are no longer directly ascribable to a specific individual" could be interpreted restrictively (i.e., as subjecting the patentability of human parts to an additional condition: anonymity). In order to clarify this amendment the Council and Commission intended to adopt a clarifying declaration. It was generally expected that such a declaration would avoid a restrictive interpretation in the sense that any patentable part which has been obtained from the human body by a technical process, would "no longer directly ascribed to a specific individual". This was acceptable to industry, although the fact the Committee could not come up with a clear text in itself was significant. Prior to the vote the European Parliament also sought to include a Declaration which ran counter to that of the Commission's and effectively restored the ambiguity of Amendment 3.

(iii) *If the Industry is of the view that a directive is needed, would a directive which excluded human DNA from patenting be acceptable?*

In industry's view, a Directive is not presently achievable in any satisfactory form. Any moves to exclude isolated human DNA from patentability would be unacceptable to industry. Europe would be put at a major competitive disadvantage to those countries e.g., United States and Japan, where patenting of isolated human genes is accepted.

2. WOULD IT BE POSSIBLE TO ALLOW PATENT PROTECTION FOR THE PROCESSES INVOLVED IN BIOTECHNOLOGICAL INVENTIONS WHILE FORBIDDING THE PATENTING OF DNA?

To allow only the patenting of biotechnology processes rather than products would be unacceptable to industry. There are several reasons for this. First, it is notoriously difficult to police infringement of process claims. Not all jurisdictions allow factory inspections or discovery of relevant documentation. Second,

experience in countries such as Spain and Italy which until recently did not permit the patenting of pharmaceutical products *per se* shows that process claims provide inadequate protection. Copyists can usually find a way to circumvent the claimed process. Third, where the invention consists of identification and isolation of useful DNA, the process for its commercial preparation is a matter of routine, and may not meet the requirement for inventive step.

The directive consequence of such inadequate protection would be the reduction in investment in research and development leading to a decrease in the development of innovative new medicines for unmet medical needs such as arthritis, cancer and neurological disorders. This would not only affect the established companies, but also the emerging biotechnology industry in the UK which would find it much harder to attract investment.

In addition to the above points, I have enclosed several papers which members of the Committee may find of interest, setting out in more detail some of the issues raised above. These include:

Background information on patenting human genes prepared by the BioIndustry Association.[1]

Copy of an Article prepared by Andrew Sheard of Kilburn & Strode on the demise of the Directive.[1]

A CBI Position Paper which discusses the question of patent harmonisation and many of the difficulties inherent in the draft Directive in more detail.[1]

I hope that the above information is of assistance to the Committee in its deliberations and if you require any further information, please do not hesitate to contact me.

Letter to the Clerk of the Committee from Professor J M Connor, University of Glasgow (HGC 160) (28 April 1995)

Alastair Kent from the Genetic Interest Group has written to me with concerns that the Committee might have misinterpreted some questions and answers in respect of whether a person with a genetic predisposition is disabled. As I recall at the time of questioning the primary emphasis related to part genetic or multifactorial disorders such as high blood pressure, premature heart disease and arthritis. Given that these common disorders of adulthood will affect most of us at some stage in our lives, there is clearly a degree of predisposition to this type of disorder in most members of the population. This type of predisposition is, however, generally weak and indeed by its very name is only part of the disease-causing process. In contrast there are the single gene disorders which although rarer have a much more direct impact on the individual carrying the altered genetic predisposition. Here a single underactive gene or pair of underactive genes will directly cause the condition in an individual and advances in genetic testing have meant that it is possible to detect such individuals prior to them developing clinical symptoms. In contrast to the part-genetic disorders, the single gene disorders thus carry a high probability that a gene carrier will develop the condition and indeed for many conditions this probability is 100 per cent and no treatment can currently avert the person developing the condition and subsequent disability. The position of GIG is that they would not wish for such genetic testing to be enforced by external agencies nor would they wish the result of such genetic testing to be used by external agencies in making decisions about life insurance, employment etc. They believe, and the Clinical Genetics Society would support, that the advances in genetic testing are for the use of individuals within families in order to make their own personal life and reproductive decisions. Hence this information should remain confidential to the individuals tested within a family and whilst those individuals shown to be at substantial risk of subsequently developing the disorder are not themselves disabled prior to the development of symptoms, they need the same type of protection against discrimination as afforded to disabled individuals under the legislation. I hope these comments help to clarify this aspect and would be happy to expand on any points if required.

Memorandum from Dr Diane McLaren, Medical Research Council (HGC 161) (6 June 1995)

FIVE YEAR SEQUENCE MAP INITIATIVE

Proposals have recently come forward from Dr John Sulston (Sanger Centre, UK) and Dr Robert Waterston (Washington University, USA) for the production of a sequence map of the human genome within the next five years. The approach will be based on technology developed by Sulston and Waterston during joint studies on the nematode (*C. elegans*) genome funded initially by MRC and NIH. It has been suggested that the human sequencing initiative might begin by focusing on one or two whole chromosomes (22 and X) to demonstrate the transferability of the planned approaches. Implementation of this initiative is presently being discussed between the MRC, the Wellcome Trust and the NIH.

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[1] Not printed.

Needless to say the project will be expensive if it is to be achieved in the proposed time scale and multi-sponsor investment will therefore be essential. The MRC was awarded additional funding of £3.5 million in 1995–96 specifically to take forward new research on the human genome. Provided the proposals put forward by Dr Sulston meet the current competitive standard at peer review, they would be a first claim against this additional money. We are at present planning on the assumption that the MRC will be committing about £2 million per annum for five years to this initiative. The level of support to be provided by the Wellcome Trust and the NIH has still to be determined.

The MRC and the Wellcome Trust are planning an open day for colleagues from industry and Europe at the Hinxton genome campus this Summer with a view to presenting a picture of Hinxton's present and future role in international genome research and identifying possibilities for improved information exchange and collaboration. We hope also to interest the attendees in contributing to the five year sequence map initiative.

Letter to the Committee Assistant from Professor Peter Harper, Head of the Institute of Medical Genetics, University of Wales College of Medicine (HGC 163) (12 June 1995)

You will remember that the potential difficulties in the event of Regional Genetic Services being devolved to GP fund holders was raised by members of your committee. At the time, we had not thought this likely since a new co-ordinating committee to oversee genetics contracts had just been set up and indeed was referred to in the discussions that your committee had. Since this visit however, we have now been informed that genetic services will be devolved to GP fund holders from April 1996, a proposal that gives us considerable concern.

As you know, the cornerstone of our all Wales service have been the high degree of equity on a geographical basis throughout Wales and the efficiency given by it being administered as a unified service, while having widely devolved clinics to enhance ease of contact with patients and families. The other key aspect has been the close integration of clinical and laboratory genetic services. We greatly fear that both these valued aspects would be lost by having to contract with GP fund holders, especially since we have been told by our contracting colleagues that this would necessitate separate arrangements for the clinical and each of the laboratory services, and that these would have to be handled separately by each of the provider units in each different hospital in Wales.

As you can imagine, the administrative complexity and fragmentation resulting from this could well be such as to render our current service unworkable. We are naturally hoping that by discussion with colleagues in Welsh Office and elsewhere, that such an outcome can be avoided, but it would indeed be sad if the unit you have chosen as an example of ways of delivering medical genetics services should be affected in this way and I feel your members may wish to take this into account before finalising the document.

Memorandum from the Office of Science and Technology (HGC 112) (2 February 1995)

INTRODUCTION

1. The Office of Science and Technology (OST) recognises the importance of human genetics research. This is an area of enormous potential value for human health and welfare and industrial competitiveness. It offers major opportunities for partnership between industry, the science base and Government, building on the strength of UK science to promote wealth creation and the quality of life.

2. The UK is a world leader in genetic science and provides a clinical environment for medical research whose value is widely recognised. The Government is determined to build up the UK infrastructure for genome biology in a way which will serve the country well into the next century. This commitment was reflected in the UK's success in bringing the European Bioinformatics Institute to Cambridge, where Hinxton Hall is becoming one of the world's leading genome research parks.

3. Further evidence comes today with the announcement of *new, additional funding* in support of high priority strategic research in genome analysis. Three point five million pounds will be provided to the Medical Research Council (MRC) in the financial year 1995–96. This represents £7 million in a full year. The money will be used to build on the research which the MRC is already undertaking in collaboration with the Wellcome Trust and will be additional to the £12 million that the MRC already expects to spend in 1995–96.

SPECIFIC QUESTIONS

What mechanisms, if any, are there by which government departments can keep abreast of any relevant developments in genetics research?

4. The Office of Science and Technology has a central role in shaping UK policy on science, engineering and technology. It does so against the background of the 1993 White Paper "Realising our Potential"[1] which established important new mechanisms for co-ordinating science, engineering and technology in the UK. The OST is playing a full part and an important co-ordinating role in relation to the science base of the UK—the area from which new advances are emanating.

5. The Technology Foresight Programme jointly conducted by industry and the science and engineering communities, will be used to inform Government's decisions and priorities and those of the private sector. The Life Sciences Foresight Panel under Professor Mark Ferguson is looking at the medical, therapeutic and diagnostic applications of human gene information. The first report by the Foresight Steering Group is due to be published in May, with individual panel reports becoming available before that.

6. The results of the Foresight Programme will be reflected in the second Forward Look of Government funded science, engineering and technology, also due to be published in May. This brings together in a single document future strategy for publicly-funded science and technology across Government. It is compiled by the Office of Science and Technology and looks ahead over a 5-10 year period. The first Forward Look, published in 1994, highlighted biotechnology, and in particular genome research, amongst the research priorities for the Department of Health (DH), the MRC and the Biotechnology and Biological Sciences Research Council (BBSRC).

7. Both exercises will take full account of the UK's strength in genetic research and the opportunities it offers for the future. They will reflect comments by the Council for Science and Technology (CST), chaired by the Chancellor of the Duchy of Lancaster. The CST brings together eminent scientists and industrialists to advise on the broad strategy for UK science, engineering and technology. The Prime Minister met the Council in September when he emphasised the importance of dialogue between Government, industry and the scientific community. The Secretary of State for Health is due to attend the Council in February.

8. Meanwhile, the OST has already taken important steps to promote genetic research in the UK. In January 1993, the Chief Scientific Adviser established an Advisory Committee on Human Genome Research. Its purpose was to kick-start co-ordinated activity in this area. Paragraphs 21 and 22 of this memorandum describe how this has been achieved.

9. In general, Government Departments are responsible for keeping abreast of developments in genetic research in their specific areas of interest. The health departments, for example, have extensive interests in human genetics. They have close links with the MRC, particularly through the concordat between them. This enables regular exchange of information on new developments.

10. Other Departments' specific mechanisms include the Home Office's national criminal DNA database, and the joint Foreign and Commonwealth Office/Home Office procedures to determine the true relationship of prospective immigrants and their children.

11. Expert Advisory Committees also play an important role. For example, DH benefits from the expert advice of the non statutory Gene Therapy Advisory Committee, which brings together a wide range of expertise in considering all proposals for gene therapy research on human subjects in the UK.

Is there a co-ordinating mechanism to ensure that such knowledge of research is widely disseminated and its implications discussed?

12. OST is concerned with policy issues rather than the specific details of research; particulars of individual research projects are best communicated through scientific networks and the publications which support them. The Chief Scientific Adviser maintains a close dialogue with appropriate bodies. He has regular meetings with other Government Departments and chairs the official Cabinet Committee on science and technology, EDS(O). He has regular contacts with the Wellcome Trust, the Association of British Pharmaceutical Industries and others.

13. One of the central themes of last year's White Paper was fostering Public Understanding of Science. Whereas specific initiatives in the biomedical sciences are for the MRC and the health departments, OST takes a co-ordinating role, with a total budget of £1 million in 1994–95.

14. Perhaps the most successful event of last year was the first ever National Science Week, SET', organised by the British Association on behalf of OST. We expect this year's event, to be held over the period 17–26 March, to be even more successful and are supporting this to the tune of £140,000. One of the MRC events scheduled for Science Week, a display in the concourse of Euston Station called "Genes Are Us", should do

[1] "Realising our Potential, a Strategy for Science, Engineering and Technology", Cm 2250.

much to increase understanding of genetics research. MRC plan to repeat this display during the Edinburgh Science Festival, when they will also be running a series of talks on "Genetics of Behaviour".

15. The Chief Executive of each of the Research Councils has the objective of improving the Council's connections with, and responsiveness to, industry and promoting public understanding of research.

16. OST played a major role, together with the MRC and the Wellcome Trust, in bringing the European Bioinformatics Institute (EBI) to the UK. Hinxton Hall near Cambridge, is now one of the foremost genome research parks in Europe housing the Sanger Centre and the Human Genome Mapping Project Resource Centre.

17. The EBI, together with the Human Genome Mapping Project Resource Centre and the MRC's Industrial Advisory Group (which serves as an interface with industry) all have a major role to play in the dissemination of information on human genetics research to the scientific community, industry and the National Health Service (NHS). The EBI is developing data libraries and high speed data networks for information derived from the Human Genome Mapping Project. Between them, these institutions serve to provide a hub for co-ordinating and disseminating information on human genome mapping research in the UK and in Europe.

18. Much human genetics research depends on population studies based on data collected through the NHS. Data derived in this way is anonymous and, subject to the usual ethical considerations, is available for research purposes. To maintain such access, the UK is pressing within the European Union (EU) to exempt medical research from provisions of the draft data protection directive which would require the "clear and unambiguous consent" of each individual from whom data was derived.

19. Some of the data obtained by commercial organisations is proprietary in nature. Discussions are currently under way in the EU to ensure reasonable access to this by research scientists.

20. The Nuffield Council on Bioethics has an important role in promoting consideration of and debate on ethical issues in genetics research, and the Government has been supportive of the initiative.

What resources does the OST devote to activities relating to such research?

21. Through its grant-in-aid to the MRC, the OST provides funds for research into human genetics, including work on the human genome. In 1994–95 the OST provided additional funding to MRC for genome mapping research. More new money will be available in Financial Year 1995–96, when a further £3.5 million will be provided to MRC to fund high priority strategic research in genome analysis. This represents an additional £7 million in a full year.

22. OST has also taken *ad hoc* initiatives. In 1993, it commissioned an independent report on the Human Genome Mapping Project in the UK which was produced by an Expert Working Group chaired by Professor Kay Davies. This was initiated by the Chief Scientific Adviser's Advisory Committee on Human Genome Research (ACHGR). The report[1] was published in April 1994 and was well received. OST will conduct a review of its impact one year after publication. This should indicate what action industry and the research community, at whom the report was largely aimed, have taken in response to the report's recommendations. The ACHGR continues to be available as an expert network to assist the Chief Scientific Adviser.

23. The OST played a pivotal role in the launch last December of the Edward Jenner Institute for Vaccine Research, which is funded jointly by the MRC, the BBSRC, DH and Glaxo plc. The Institute will undertake basic research to underpin the development of new and improved vaccines. This represents an important example of partnership between Government, industry and the science base which should lead to significant improvements in the quality of life.

Does the OST seek to play a co-ordinating role for other departments and Research Councils?

24. The role of OST in co-ordinating and shaping policy on science, engineering and technology has already been described (paragraphs 4-8). This includes major new initiatives such as the Technology Foresight Programme and the Forward Look.

25. *LINK* is a further well-established framework for collaborative research co-ordinated by OST. It seeks to promote partnership between UK industry and the research base, thereby aiding innovation and wealth creation. There are LINK programmes in bio-transformation, protein engineering, biochemical engineering, molecular sensors, medical implants and cell engineering. The LINK initiative is currently under review and there are plans to re-launch it shortly.

26. At the policy level, the OST chairs, and provides the secretariat for, the Interdepartmental Group on Genetic Modification Technology. This comprises representatives from Departments and Research Councils with an interest in gene technology.

[1] "The Human Genome Mapping Project in the UK: Priorities and Opportunities in Genome Research", London, HMSO.

At what level are issues relating to Human Genetics dealt with within OST?

27. The Chief Scientific Adviser takes a close interest in developments in this area. The Interdepartmental Group on Genetic Modification Technology is chaired by the Head of OST's Transdepartmental Group (Grade 3). Policy support is provided by other officers in OST.

28. As indicated above, OST's main role is to promote co-ordination and partnership in research in line with the policies of the White Paper "Realising Our Potential". OST has an interest in general biotechnology and health policy issues including regulation and ethical issues, but does not normally deal with matters of scientific detail.

What action has been taken or is anticipated in response to the report on "The Human Genome Project in the UK" produced by Professor Kay Davies this April?

29. This has been covered in paragraph 22.

Memorandum from Professor K Arrow, Stanford University (HGC 121)

MEDICAL INFORMATION AND MEDICAL INSURANCE: AN ETHICAL DILEMMA

1. Introduction

In the rather peculiar system of medical insurance prevailing in the United States, a conflict, partly ethical in nature, arises in improving the accuracy of medical diagnosis and prognosis. The conflict is especially acute with regard to genetic testing. The problem is this: Medical insurance for employees is supplied by employers. Each employer is free to choose his or her own plan and indeed free to change it from time to time. The plans are contracts with insurance companies, though in many cases the employer bears some part of the risk. Suppose medical indications of an employee are found which show, definitely or with high probability, that he or she will incur large medical expenditures. Then an insurer will have an incentive to deny further insurance to the employee or at least charge a higher premium. This is especially likely to take place if the employee moves to another job. The new employer will either not be able to insure the individual or have to pay the higher premium, and therefore will not wish to hire him or her. The upshot is that both through possible denial of insurance and through restrictions on labour mobility the medical information has caused a disadvantage to the individual.

Yet it is our usual intuition that increased information is better both for prudential and for ethical choice. We seem to find ourselves in the ethical dilemma of either forbidding the use of available diagnostic and prognostic techniques in some cases or of running the risk that their use may be harmful to the patient.

I will argue that there is in fact a way out of what I will term the Information Dilemma but at a price, namely, that available information cannot be used for some purposes. I will spell out in more detail in what situations the Information Dilemma can arise. In Section 2, I describe the relevant aspects of the United States medical insurance system. In Sections 3 and 4, I will develop in greater detail the kinds of risks to which insurance, in the most general sense, is applicable, and argue that a fuller consideration of the nature of risks clarifies the nature of the dilemma. I will then suggest an ethically valid solution. Section 5 is devoted to a reconsideration of the Information Dilemma from the viewpoint of ideal competitive markets, which, under certain circumstances, can achieve Pareto efficient outcomes, which, by definition, meet at least some ethical criteria. It is argued that ideal markets would, as usual, resolve the ethics of the Information Dilemma but many of the necessary markets do not exist and are not likely to be capable of existence.

The particular dilemma arising from the interaction between increasing prognostic ability of medicine and employer-based medical insurance is not relevant to universal coverage, such as exists in most parts of the advanced world. But the ethical issues arising from incomplete insurance markets have other domains of application, which will be explored briefly in Section 6.

2. Medical insurance in the United States

In the United States, a very characteristic medical insurance policy is a contract between a firm and an insurance company, by which the insurer assumes the risks of health care of the firm's employees under prescribed conditions. In return, the firm pays a premium. The premium paid by the firm is regarded for the purposes of corporate income taxation as an allowable business expense. On the other hand, the provision of

the medical coverage is not regarded as taxable income to the employees. Hence, the employees have a preference for medical coverage over a wage payment equal to the premium.

The medical insurance coverage is purely voluntary on the part of the firm; of course, it may be part of a collective bargaining agreement. The tax system, as just seen, supplies strong inducements, but, even so, many firms, particularly smaller ones, do not offer the insurance. As a result, about 11 per cent of the United States population is in the position of working and ineligible for medical aid to indigent persons but not covered by medical insurance.

Since the medical insurance is voluntary, its terms are determined by the insurer and the insured firm. They differ considerably from one employer to another. The same employer may vary the terms of the contract over time. Since medical costs and therefore premiums on insurance policies have been rising rapidly, firms are under increasing incentive to reduce medical coverage and have been doing so.

In some United States employer-based medical insurance, the employer bears some or all of the risks. In the extreme case, the insurance company is simply an administrator; the firm simply self-insures. This is permitted by law and in fact has some tax advantages. Again, the company is free to change the terms of its insurance policy. Recently, a relatively small company (about 50 employees) which self-insured had a claim for treatment of AIDS, provided for under the terms of the policy. The firm promptly changed its policy to set a very low ceiling of reimbursement for AIDS treatment, and this change was upheld by the courts under existing law.

Even when the firm is not completely self-insured, the firm frequently bears some of the risks. If its experience has been unusually good or unusually bad, future premiums are very likely to reflect this experience, and at some level a good case can be made that they should. Only for very large firms does the law of large numbers imply that the experience is apt to be relatively constant.

What has been just described is, in some sense, the normative position in United States medical insurance, but in fact there is a great deal of medical coverage under other provisions. Some individuals, especially self-employed, have medical insurance on their own; this however is not very large in magnitude. More important is special coverage for the indigent, so-called Medicaid, operated by the individual states with some reimbursement from the Federal government, and above all for the retired, called Medicare, financed out of the Social Security fund (retirement pensions). The Information Dilemma pertains to employer- and individually-based insurance policies, not to the governmentally-supported programmes.

3. Prognosis, pre-existing conditions, and the scope of medical risks

When an insurance policy is taken out, it is natural for the insurer to use all available information to evaluate its risks and set its premiums accordingly. This might seem to be socially efficient and in many contexts is. Therefore, upon any renewal of a medical insurance policy, the insurance company will want to take account of the particular medical conditions of the employees being covered, especially for small firms where even a few patients with unusually large expenses may change medical costs appreciably.

Hence, an insurance company will want information on existing diseases which give rise to future medical expenditures. Typically, the insurer is and continues to be responsible for medical costs of employees who continue to be employed in the same firm, although the case cited above shows that there may be rights to alter their coverage. But certainly the pricing of a new employee's insurance may be contingent on his to her medical condition. Thus hiring new workers with pre-existing medical conditions which need further treatment will cause an increase in the firm's medical premiums.

The employer now has an incentive not to hire workers with pre-existing medical conditions. This incentive is all the stronger to the extent that the firm is itself bearing all or part of the medical risks. What has evolved is a common provision in medical insurance policies that pre-existing conditions are not covered, at least not for a period of time which may last several years.

This already violates to some extent the idea of medical insurance. Illness has become costly to the individual worker. He or she might avoid the cost by staying with the original company, but this tactic certainly is costly if opportunities are better. It is also socially inefficient in restricting the mobility of labour, by which labour is allocated to its best use.

Loss of insurance coverage for pre-existing conditions is the simplest case of a dilemma which might easily become much more serious. In the case of pre-existing conditions, the information about the individual is already in existence. Suppose the employee, perhaps as part of a general checkup, undertakes some tests even in the absence of overt symptoms. These tests may reveal a pathology not yet manifest, e.g., an HIV-positive reading or abnormal cardiac rhythms. There is now a prognosis of disease or at least a greatly increased probability of the need for treatment. If this information is available to the insurer, it will very reasonably take it into account and set higher premiums or even restrict coverage to minimise the financial impact on it. Hence, the additional information may turn out to affect the employee adversely.

We think of knowledge about oneself as an ethical imperative. In any case, it may well be very useful, for example, in permitting early treatment or preventive steps, such as changing one's activities to avoid strains. Yet the workings of the medical insurance system mean that getting information through tests creates a risk of adverse financial consequences, some of which might indeed be very severe. This is the Information Dilemma.

It has been argued that the Dilemma is severely compounded by the improved possibility of genetic tests. For example, it is generally held today that colon cancer involves several distinct mutations before it occurs. A test which reveals one such mutation shows an increased probability of colon cancer. Clearly, such information can seriously alter the terms on which medical insurance is offered if the insurers, whether insurance companies or the firms themselves, use this information rationally. Even more extreme are the effects of genetic testing at birth. It is possible to predict the onset of certain diseases and at least change drastically the estimates of the probabilities of other diseases, such as cystic fibrosis and Huntington's chorea.

Although the Information Dilemma has been dramatised by the presence of genetic testing, my view is that it exists today with presently available prognostic information. The dilemma is stark. Improved prognosis is frequently beneficial to the patient or potential patient and in any case is part of our search for truth. But in the actually existing system of medical insurance, prognosis may be costly to the patient in terms of medical insurance premiums, denial of coverage, and inability to get new jobs.

Before discussing remedies, one may probe more deeply into the structure of the Dilemma. After all, the superior efficiency of free contracting is a staple of economic theory; and surely contracts ought to be arrived at on the basis of the best possible information. How can there be a dilemma?

The answer is that in fact there are risks other than medical costs. In the insurance system I have described, the individual employee and potential patient bears now the risk of a future unfavourable prognosis which affects his or her insurance status. To complete the provision of protection against risks, it would be necessary to cover what may be termed *prognostic risks*. When undergoing a series of tests, the employee realises that if they give unfavourable prognoses, he or she will have to suffer the economic losses described above. If the employee wishes to avoid risks, he or she would want to buy insurance against an unfavourable prognosis. If such insurance were available, then there would be no problem in using the prognostic information freely, and the dilemma would be resolved.

It is therefore the absence of insurance against prognostic risks which creates the Information Dilemma. We will not explore here why there is no such insurance, and indeed it may not be impossible to devise appropriate insurance institutions. But I proceed on the assumption that they do not now exist. Can we modify the existing insurance policies to achieve much the same effect.

Suppose we had prognostic risk insurance. To illustrate, make the following simplifying assumptions. (1) The standard medical insurance premium is $2,000 a year, paid directly by the employee. (2) There is a test procedure which can detect an asymptomatic illness. There is no current evidence that the employee has this illness. (3) The illness is known to have an incidence of 1 per cent in the population. (4) The illness will last just one year, if the employee has the illness, the premium needed to cover the expected costs for the coming year is now $12,000. Then before undergoing the test, the employee would want to take out insurance against the possibility of an adverse prognosis. He or she will want to take out insurance for $10,000 (the extra premium). With a probability of 1 per cent for this diagnosis, the actuarially fair premium will be $100. The actual premium will, of course, be higher to account for the costs of the insurance transaction.

Clearly, an equivalent result would be obtained if the insurance company charges $2,100 rather than $2,000 and agrees that it would disregard the outcome of the test in setting the premium. This argument suggests the following ethically and practically valid resolution of the Information Dilemma: *The information obtained in prognostic tests should be disregarded in setting insurance premiums.*

4. Ideal competitive markets in risk-bearing

Since the whole discussion has been in the context of markets, markets for medical services and markets for insurance, it is useful to ask if the standard economic analysis of the efficiency of markets is applicable. The typical, if loose, statement is that a comprehensive market system achieves an *efficient* allocation of resources. The word, "efficient," has a sharply-defined meaning, first clarified by the great Italian economist, Vilfredo Pareto. It means that there is no other way of using the same basic resources (labour, capital, land, raw materials, and so forth) in some other mode of production and distribution of final goods to the members of the economy so that everyone is made better off.

The basic conclusion of economic theory, in the branch called welfare economics, is that a system of markets *which cover all possible commodities* and which operate competitively will have as its outcome an efficient allocation of resources. The underlined phrase is essential to the validity of the conclusion. If not all commodities can be bought and sold, then it is certainly not true that permitting some markets will lead to an efficient allocation. In fact, surprising as it may seem, if some markets do not exist, opening some other markets does not necessarily increase efficiency.

The concept that a market may not exist may sound a bit odd. The interesting cases, as we shall see, relate to financial markets, including those for risk-bearing, which require some explanation. However, one simple example is that of road transportation and specifically of highway availability. A firm, in order to expand its business, will require more trucking to take away its product to the point of delivery. But the roads available are supplied by the local government. There may, for example, be considerable congestion, so that the firm cannot ship more only with difficulty. It might be very willing to pay for the additional road capacity if it were earmarked for its own use, but no market exists on which it can buy such capacity.

In a world of risks, a firm or individual will usually want to purchase some insurance. We can put the matter by saying there are markets on which one can buy or sell bets on any possible uncertain event. Then welfare economics tells us that efficiency is attainable if markets are available for all possible risks. Note that insurance against medical costs is one such market. We can have separate markets for each state of information about the present and predicted health of those insured. This would permit medical insurance policies whose terms depend on prognostic information. But if there are no markets for prognostic risks, then the refinement of the insurance market to take account of prognostic information may and in fact does decrease the efficiency of the economy.

To summarise, then, in a complete set of risk-bearing markets, and therefore in an efficient allocation of risks, there would be insurance against medical costs, with premiums reflecting the most up-to-date prognostic information, but there would also be insurance against what will be learned in a prognostic test. In the absence of the latter information it will be better to prohibit the use of this information in determining the premium or the availability of insurance. There is therefore a strong case for prohibiting discrimination in medical insurance on the basis of pre-existing conditions or any other tests which predict the future course of medical costs for the individual.

5. The generality of the information dilemma

The Information Dilemma has been shown to arise in the application of medical insurance in the United States system. It would not arise in an insurance system based on compulsory universal coverage. It might be thought, therefore, to be a narrow phenomenon.

I believe this is not so. In fact, very similar problems arise in financial markets. In the United States, and I believe in other financial systems, stock trading on what is called "inside information" is forbidden. That is, officers and directors of a corporation who receive some significant news, good or bad, about the prospects of the firm in the course of their duties are not allowed to buy or sell the stock until the news has been publicly announced.

Acting quickly on new information, even if it is not inside information, can be a considerable source of profit. This creates an incentive to invest very considerably in money and attention in getting news early and acting on it quickly. But there is little social value in this quick response, and there can be considerable social loss, for two reasons: (1) the investment in effort by very able people in beating others rather than in production; and (2) the market responses become more erratic and therefore discourage investment in it. In the case of the stock market, we cannot forbid investors to acquire information or to use it once acquired. It has been proposed instead to create incentives for slower responses, such as a tax on stock market transactions.

A fuller discussion will permit many other examples of the Information Dilemma in economics. Instead, let me conclude by raising the less economic question of the physician's obligation to full disclosure of information to the patient. I do think that in the normal case the physician should disclose any firmly-established diagnosis or prognosis. But suppose the physician has some information which is not conclusive and expects to learn more by further tests or by waiting. Full disclosure would require that at every stage in this process the physician should inform the patient of his or her best guess, with some indication of uncertainty. This stream of changing news can easily cause a costly alternation of hopes and fears in the patient. There is justification for some withholding of information.

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