BORN IMPERFECT

THE ROLE OF GENETIC DISEASE

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INTRODUCTION

The area of genetics in relation to hereditary disease has become an important aspect of medical practice with potentially far-reaching ramifications. We all inherit many features from our parents such as eye colour, hair colour, facial characteristics and even height and build to some extent. However, we may also inherit less desirable traits such as hereditary disease (see Box 1 for biological background material and Box 2 for types of inheritance). Genetic counselling at its most fundamental level is aimed at helping couples make an informed decision. Where they understand the risks the great majority of couples will tend towards the prevention of the birth of a child with an inherited disease, especially where the disease is severe and seriously limiting (RCP London, 1989).

Progressively infectious and nutritional diseases have been effectively controlled or eliminated in the Western world and poor social and environmental conditions ameliorated. Inevitably, and in contrast, genetic disease has not shared this improvement and hence has become a major problem. Genetic diseases have thus become relatively more important and are now, especially among children, a major cause of hospital admission, disability and mortality. The following information may demonstrate this point: in 1940 for every one child who died from a genetic disease six children died from infectious diarrhoea; whereas in 1980 seven children died from a genetic disease for every one child who died from infectious diarrhoea (Garver, Marchese 1986). The same type of comparison could be made for a number of infectious ailments which are no longer the threat to human life that they once were.

The number of women who conceive an embryo with a chromosomal abnormality is by no means insignificant. It is estimated that about 50 per cent of women do so at sometime in their reproductive life. However, most of these pregnancies end in spontaneous abortion (miscarriage) and indeed some may end so soon after conception that the woman may not have even realised that she was pregnant (RCP, 1989). Nevertheless, about two to three per cent of full term pregnancies carry congenital malformations or genetic abnormalities at the time of birth (Fuhrman and Vogel, 1983). During a lifetime the proportion of affected persons will be much higher since many abnormalities are not present at birth.

Genetic disorders place considerable health and economic burdens not only on affected people and their families but also on the community as a whole. As other forms of disease are controlled those that are wholly or partly genetically determined are becoming more

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important. Such disorders account for about one-third of all admissions to paediatric wards (Kingston, 1989).

Genetic counselling

The aims of genetic counselling may be summarised as follows: to establish an accurate diagnosis, to provide information about prognosis and the risk of developing or transmitting a disorder, and to suggest ways in which it may be prevented or ameliorated and thus to help couples to make an informed decision. Clarke (1991) suggests that one of the primary aims of medical geneticists concerns the welfare of those with genetic disorders, but not the prevention of genetic disease by termination of pregnancy. This point is reinforced by Pembrey (1991) who claims that 'there is already consensus that reduction of the birth incidence of genetic disorders is not the object of genetic services'. Nevertheless, clinical genetics services have faced growing demand as both the medical profession and the general population have become increasingly aware of the genetic contribution to disease and the potential for identifying those at risk and for prevention.

Since most genetically inherited diseases are not presently amenable to treatment the current emphasis is placed on prevention of genetic disease. However, often counselling is only contemplated after the birth of an affected child. A major problem in this field is that most infants with congenital or chromosomal disorders are born to healthy young mothers with no previously identifiable risk factors – this is partly explained by the fact that about 40 per cent of pregnant women in the increased risk age range (over 35 years) abort pregnancies for personal reasons so that many potentially affected children are not actually born (see Box 3 for changes in attitudes towards birth control and abortion over time). Thus, there can be seen to be two central aspects to the problem of genetic disease. Firstly, the issue of 'predictable' genetic disease where there is clear evidence of an inheritance pattern and where one or both parents are carriers of the defective gene. Secondly, the unpredictable cases of congenital disease where both parents of an affected child appear to be normal and the abnormality seems to be a random occurrence, due either to an arbitrary mutation or to some kind of environmental factor. (This category may erroneously include children of asymptomatic carrier parents where the genetic cause of disease may be masked by the apparent good health of the parents). The only solution here would be cheap, accurate and safe mass screening of all pregnant women prepared to accept it whether or not they have identifiable risk factors.

The person performing the genetic counselling must be both knowledgeable of the genetic facts and be able to communicate these to the affected person or couple at a level that they can understand and utilize. All the medical, social and economic aspects of these conditions should be thoroughly discussed. Genetic counselling should be non-directive, in that, the counsellors should respect the diverse ethical, moral and ethnic backgrounds of their patients and realise that the patients decision may not be the one that they would have chosen. The counselling should merely point out the consequences of different actions without directing the decision towards a particular conclusion.

Molecular genetics

Spectacular advances in molecular genetics, and their application in the understanding of human development and disease have gained considerable public attention. Indeed an Editorial (1992) in Nature went as far to ask 'has the whole of research been abandoned for genetics?.... General newspapers are full of genetics, sometimes sensationally so...' A world-wide project to map and sequence the genetic complement of man is currently in operation. Scientists are starting to read the fundamental blueprint that encodes the characteristics of a human being. The complexity of this project is awesome requiring the latest high-powered computer technology to carry out the repetitive aspects of this work. The international programme to map and sequence the entire human genome has considerable implications for clinical and preventive medicine; indeed molecular techniques have already revolutionised the treatment of some genetic disorders. Roy Herbert (1992) described the human genome project as 'surely the most stupendous task ever started by mankind'. The need for genetic counselling will expand exponentially as screening programmes and public awareness increases about the medical, societal, economic and ethical implications of medical genetics (RCP, 1991).

The UK has it own 'Human Genome Mapping Project' established in 1989 with funds from the Medical Research Council. Professor Wolpert (1991) says 'there is real cause for optimism that the programme will continue to maintain the UK at the forefront of the world-wide effort to characterise the human genome'.

Gene therapy

Gene therapy, which has been dubbed 'the next revolution in medical science', is an experimental treatment whereby normal genes are implanted into a patient to overcome diseases caused by defective

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genes. Gene therapy could take several forms. It may attempt to correct part of an abnormal gene to make it function again; or remove the abnormal gene and replace it with a normal one; or simply insert a normal one, so that the necessary gene product is made, while leaving the abnormal gene in place within the cells. The latter approach, whilst the least sophisticated, at this early stage of development looks like being the most practicable one. Gene therapy has been given a qualified stamp of approval by a government committee who concluded that there were no ethical objections to gene therapy but the therapy should only be used to treat disease not to enhance normal characteristics such as height or altering eye colour (The Clothier Report, 1992).

Rapid progress in the development of new techniques for diagnosis of disease carriers, prenatal diagnosis, the cloning of disease genes and the emergence of gene therapy show how worthwhile the fields of enquiry into hereditary disease and genetic counselling, screening and therapy have become. Any study of this type should involve consideration of the controversial and contentious issues inherent in this subject which raises many practical, ethical and religious dilemmas. Genetic counselling has implications for economic costs to the health service, the community and affected people's families as well as for the possible reduction in personal suffering and pain to the affected individual and the burden of care to their families which is often financially draining and emotionally and physically exhausting.

BOX 1 **Basic Biology of Inheritance**

The human organism is composed of millions of cells. The nucleus is present in most of these cells and contains chromosomes. The major constituent of these chromosomes is deoxyribonucleic acid (DNA). DNA is the macromolecule that stores genetic information which leads to the production of a familiar set of proteins. Genes are present in all 46 human chromosomes. Two are sex chromosomes and the remainder are known as autosomes (22 pairs or 44 autosomes). Everyone inherits two copies of virtually every gene: one from their mother and one from their father. Traits determined by the information on these chromosomes are called autosomally inherited. The autosomes pair according to their size and shape and the members contain the same gene loci (homologous chromosomes). If both genes in a pair at the same loci possess the same genetic information the individual is homozygous (identical). However, gene loci may have altered (changed or mutated) genetic information; one allele on one gene locus may be different from the corresponding chromosome. In such cases the individual will be heterozygous (different). Individuals can thus be homozygous for normal gene, homozygous for the defective gene, or may possess one normal gene and one defective gene in a single dose, that is, heterozygous for the particular gene locus (Box 2 will demonstrate the importance of these genetic states for inherited disease).

The chromosomal – as opposed to genetic – constitution of an individual can be determined by studying peripheral blood. Two ml of blood can be withdrawn and placed in a heparinized tube, and eight to 10 drops are placed in culture for 72 hours. Usually each lymphocyte cell in the blood sample will contain 46 chromosomes that can be separated into two groups: autosomes and sex chromosomes. Regarding the latter a normal female will have two XX chromosomes and a male an X and a Y. Thus, 46, XX indicates a normal female and 46, XY a normal male; whereas, 47, XX, +21, would indicate a female with an extra 21 chromosome (that is, a female with Down's syndrome).

BOX 2 **Types of Inheritance**

There are several principal types of inheritance that need to be clearly defined. Firstly, there are autosomal dominant disorders with a clear pattern of inheritance and a high risk to relatives. This means only one of the parents need possess the defective gene for the disease to manifest itself in offspring. Thus, to be affected a person need only be heterozygous for the defective gene (ie. one of the alleles for the same gene locus is normal and the other one is defective). Affected individuals transmit the disease to half their offspring affecting both males and females. Unaffected (disease-free) family members cannot transmit such disorders, since one must have the disease in order to pass it onto heirs, and hence their offspring are not at any increased risk. Autosomal dominant disorders are the most common type of inherited disease. A particular problem with some dominant diseases is that they do not manifest themselves in affected persons until most have completed their own families. For example, sufferers from Huntington's chorea and polycystic kidney disease often do not show any symptoms until the individuals are of an age to have completed their own families and thus may inadvertently pass on their disorder to their offspring while they are still asymptomatic and apparently healthy. Diseases which are inherited in an autosomal dominant manner include: Familial hypercholestolerolemia, Myotonic dystrophy and Tuberous sclerosis.

Secondly, there are autosomal recessive disorders whereby the child must inherit the defective gene from both parents for the disease to manifest itself. This means the child must be homozygous for the defective gene (ie. to become affected they must possess two defective alleles for the same gene locus). When two parents carry a single defective gene at any particular locus, whilst they themselves appear healthy, the risk to their offspring of manifesting the disease is one in four, but there is a two in three chance that their normal children will be carriers (ie. inherit one defective gene for that loci). The degree of consanguinity (ie. how related the couple are, for example, they may be cousins) between the parents may point to an autosomal recessive mode of inheritance, since the same defective gene may have come from a common ancestor. Autosomal recessive disorders include: Cystic Fibrosis (CF), Sickle cell disease and Tay-Sachs disease. It is perhaps useful to highlight a sub-group of recessively inherited known as X-linked recessive disorders. These affect only males, the disorder being transmitted via healthy female carriers. A female carrier will transmit the disorder to half her sons and half her daughters will be carriers. All the daughters of affected males are carriers; whereas sons are unaffected. X-linked recessive disorders include Becker's and Duchenne muscular dystrophy, haemophilia A and B and Fabry's disease.

Thirdly, there are multifactorial diseases such as heart disease and some cancers[1] which may show a familial predisposition but no clear pattern of inheritance and environmental factors, for example, diet and lifestyle may play a major role. There are a number of ailments which could fall into this final category because they are not wholly determined by inheritance but do have some degree of heritability. Disorders such as schizophrenia and asthma are thought to have an appreciable genetic contribution in a substantial proportion

1 Some types of cancer can show a clear inheritance pattern, e.g. neurofibromatosis which can be inherited as an autosomal dominant trait. Nevertheless, about half the cases of neurofibromatosis arise from spontaneous mutation rather than from inheriting a mutated gene.

of cases. Between two thirds and three quarters of cleft lip and palate and coronary heart disease cases can be assumed to have a significant inherited component. Genetic contribution is less likely but may nevertheless be important in hypertension and neural tube defect where over half of the cases can be at least partially due to inheritance.

Finally, largely unrelated to any inherited characteristics, there are also children born with congenital abnormalities which are essentially random and unpredictable. One of the most common reasons for such an occurrence is new mutation, for example, whilst approximately 70 per cent of X-linked muscular dystrophy cases do have a clear pattern of inheritance about one in three cases are due to a new mutation. A gene may have mutated in a germ cell of either of the parents, and should this cell be fertilized, the mutant will combine with its counterpart in the other germ cell. The child will be heterozygous for the mutation in question. Should the mutation be for an autosomal dominant disease, the disease will manifest itself in the child and about half its descendants. A new mutation is an isolated occurrence with no increased risk to subsequent children unless the cause is environmental. There is still no increased risk to subsequent children provided the environmental cause can be identified and eliminated in future pregnancies.

Table 1 provides some examples of how inheritance can play a role in the transmission of certain diseases. There are also some multifactorial diseases listed which may have an inherited element as well as an environmental or lifestyle factor.

Table 1 **Examples of how inheritance can give rise to some disorders**

Mode of Inheritance	Condition	Symptoms	Time of onset
Autosomal dominant	Tuberous sclerosis	Retarded/epileptic/ tumours	Birth
	Myotonic dystrophy	Deformations of musculoskeletal system	Birth-adolescence
	Familial hyper-cholesterolaemia	Coronary heart disease	20s-30s
	Huntington's chorea	Involuntary movement/dementia	35-45
	Adult polycystic kidney disease	Cysts in liver/pancreas/ spleen/kidney	40-60
Autosomal recessive	Cystic fibrosis	Failure to gain weight/ attacks of bronchitis	Birth
	Sickle Cell Anaemia	Chronic anaemia/ infections/painful or hemolytic crises	Birth
	Thalassaemia	Severe anaemia/skeletal deformity	Birth
	Tay-Sachs Disease	Deafness/blindness/ seizures/spasticity	3-6 months
	Hurler's syndrome	Retardation/deformity/ deafness/dwarfism	1st year

Mode of Inheritance	Condition	Symptoms	Time of onset
Multifactorial[2] Often high genetic contribution	Asthma	Difficulty breathing	Birth
	Schizophrenia	Hallucinations/ 'crazy' behaviour	Usually adult
	Coronary artery heart disease[3]	Arteries narrow can lead to heart failure	Usually late
	Hypertension	High blood pressure	Late
Multifactorial Can have some genetic element	Peptic ulcer	Ulcers in the stomach and duodenum	Late

2 Multifactorial inheritance of disease implies that the interaction of several adverse genetic and environmental factors lead to the manifestation of disease.

3 Familial hypercholesterolaemia may account for up to 10 per cent of all early coronary heart disease (Kingston, 1989), the remainder may be due to lifestyle and/or a genetic predisposition for heart disease.

BOX 3 **Changes in Social Attitudes**

Attitudes towards many social issues, such as abortion, birth control and premarital sex have altered a great deal in the past 30 years. For example, more than 40 per cent of pregnancies in mothers over the age of 35 are now aborted for social reasons (RCP – London, 1989). The following extract from a piece written by Karl Barth in 1961 demonstrates this change in attitudes over time. He claimed that 'no community, whether family, village or state is really strong if it will not carry its weak and even its weakest members. They belong to it no less than the strong, and the quiet work of their maintenance and care, which might seem useless on a superficial view, is perhaps more effective than common labour, culture or historical conflict in knitting it closely and securely together. On the other hand, a community which regards and treats its weakest members as a hindrance, and even proceeds to their extermination is on the verge of collapse'. Perhaps in the 1990s many people no longer view the prospect of preventing 'weak' members of the community coming into existence as something detrimental to society as a whole. Fletcher (1986) argues that human ethical guidance undergoes an evolutionary process. 'Ethical thought', he suggests, 'is influenced by technological possibilities, because what can be done implies what ought to be done'. In open societies Fletcher sees law, science, technology and ethics closely bound together in a coevolving process. It is thus perhaps not surprising that social norms and values appear to have altered a great deal. The relatively short period of time in which this has happened is probably more startling – perhaps reflecting rapid advances in science and technology during this period.

Sources: Garver, Marchese (1986); RCP, London (1989); Fletcher (1986).

THE DEVELOPMENT OF GENETICS: A HISTORICAL PERSPECTIVE

The notion that one could improve humanity by interfering with genes was popular long before technical progress helped to illuminate this area of medical science. Dr Steve Jones in the final 1991 Reith Lecture describes how Francis Galton, a cousin of Charles Darwin, in his book 'Hereditary Genius' marked the beginning of human genetics. He claimed that a tendency for genius cropped up in certain families again and again, suggesting to him that ability was inborn. Galton founded the 'science' of eugenics whose aim was to 'check the birth of the unfit and improve the race by furthering the productivity of the fit by early marriages of the best stock'. The proponents of eugenics shared some highly heritable traits: wealth, education and social position.

The Paraguayan village of New Germany houses some descendants from an experiment aimed at improving humanity. Their ancestors came from Saxony in 1886 chosen by Elizabeth Nietzsche as particularly splendid specimens of 'German purity'. They were to be the beginning of a new race of superhumans; today these inhabitants of New Germany are poor, inbred and suffer inherited disease.

As long ago as 1,000 BC the Jews recognised the problem of inherited disease and they allowed a mother not to circumcise her son if an older brother had bled badly at the operation; indeed even if her sister's sons had had such complications a circumcision could be excused.

However, it was not until the twentieth century that the first academic contribution to the genetic map was made by Bell and Haldane (1937) by measuring the genetic distance between colour blindness and haemophilia. They also first discussed the possibility of using linked markers with respect to the prevention and avoidance of genetic disease. Thereafter there was a pitifully slow development in the human gene map and the use of linked markers in diagnosing genetic disease 'remained a pious hope included in the final paragraph of a grant application form' (Robson, 1991).

It is nearly 40 years since Tijo and Levan (1956) discovered that the normal chromosome number in man was 46 and not 48. The importance of this to genetic disease was not appreciated until 1959 when Lejeune reported an extra chromosome 21 in Down's syndrome. However, in those days methods of chromosome identification were too crude to recognise any more than very gross changes in chromosome length.

The Medical Research Council had established a Human Genetics

Table 2 **Examples of disorders mapped to defects at specific chromosomes**

Disorder	Defect at chromosome number
Gaucher's disease	1
von Hippel-Lindau disease	3
Huntington's chorea	4
Cystic fibrosis	7
Sickle cell anaemia and B Thalassaemia	11
Phenylketonuria	12
Retinoblastoma	13
Tay-Sachs disease	15
a Thalassaemia	16
Adult polycystic kidney disease	16
Neurofibromatosis (peripheral)	17
Familial hypercholesterolaemia	19
Myotonic dystrophy	19
Alzheimer's disease (familial)	21
Hurler's syndrome	22
Neurofibromatosis (central)	22

Adapted from: Kingston (1989)

Committee as early as 1932, and by the 1960s there were a number of centres involved in genetics research. However, it was not until the 1980s that gene mapping really progressed; it has continued to develop rapidly in the 1990s (Table 2 provides some examples of disorders mapped to defects at specific chromosomes). The techniques of recombinant DNA greatly advanced the study of molecular genetics of many diseases and allowed the earlier aspirations of pioneers in this field to be put into practice.

The most recent significant advance in this area of medical practice concerns the notion of gene therapy. 'Unexpectedly rapid advances in basic science suggest that gene therapy for a whole host of diseases will soon be a medical reality' (Culliton, 1991). The Clothier report (1992) states that 'the prospect of gene therapy is obviously attractive if it can make good the genetic defects responsible, and thereby cure or alleviate disorders in which the outcomes are so dismal'. Moreover the introduction of gene therapy would serve to enhance and augment the choices open to parents at high risk of transmitting a serious genetic disorder to their children. Gene therapy based on inserting a normal gene, so that the necessary gene product is made, leaving the abnormal gene in place within the cells, seems in these early stages of gene therapy evolution to be the most practicable, if not the most refined, method.

A distinction ought to be drawn between germ line gene therapy and somatic cell gene therapy. The genes carried by each of these two kinds of cell have distinct roles, and the difference is very important. Genes carried by germ line cells can be transmitted to offspring and successive generations. Genes carried by somatic cells have their own role in those cells within the tissues and organs of the individual. It is believed that any alteration to the genes of the somatic cells will affect only that individual whereas altering genes of germ line cells may also affect offspring. The Clothier report (1992) suggests that germ line gene therapy needs to be considered quite separately from somatic cell gene therapy because so little is known about the possible consequences and hazards to future generations which germ line gene therapy may cause.

The BMA report (Our Genetic Future, 1992) says 'at present, for a number of reasons there is a general consensus that germ-line gene therapy is unacceptable'. One reason to oppose germ-line gene therapy is because it may not be wholly desirable to remove carrier potential of some diseases from the population. Carriers of sickle-cell anaemia, for example, originated from tropical Africa and the Mediterranean and were protected from malaria due to their carrier status. As a result they had a survival advantage over both individuals with two normal genes and those with two defective genes for this allele. Germ-line gene therapy would attempt to eradicate the sickle-cell gene but would also remove the benefits that the gene confers. Of course, such benefits are largely irrelevant to those carriers in North America and Europe. However, the incidence of the gene in the USA is now declining because there is no advantage conferred to carriers in the USA.

The idea has been under consideration for most of the past two decades that one could cure genetic disease by giving patients a functioning version of a defective gene. The first trial of gene therapy took place in 1990 at the National Institutes of Health in the USA. A four-year old girl with a lethal immune disorder (adenosine deaminase deficiency) was transfused with lymphocytes bearing the ADA gene. The operation was deemed a success and the child was doing well a year post-operatively. 'Gene therapy will become a new and potent force in medicine, with application to diseases as diverse as heart disease, cancer in its many forms, liver disease and diabetes – among others' (Culliton, 1991).

A five-year old child treated in Italy suffering from the same potentially fatal inherited disease as the young girl treated at the National Institutes of Health became the first person to receive 'advanced gene therapy' whereby genes were transplanted into the

Table 3 **Diseases caused by single gene defects: current targets for gene therapy[4]**

Disease	Defective gene
Immunodeficiency	Adenosine deaminase
	Purine nucleoside phosphorylase
Hypercholesterolaemia	LDL receptor
Haemophilia	Factor IX
	Factor VIII
Gaucher's disease	Glucocerebrosidase
Cystic fibrosis	Cystic fibrosis transmembrane regulator
Phenylketonuria	Phenylalanine hydroxylase
Muscular dystrophy	Dystrophin
Thalassaemia	B-globin
Sickle cell anaemia	B-globin

Source: A. Dusty Miller (1992)

stem cells which in theory have an unlimited life span. The Americans transplanted the genes into cells which only live for a few months thus the treatment will have to be repeated whereas, if successful, the Italian child will require no repeated transplants (McGourty, 1992). Table 3 provides a list of some of the diseases which may be able to be tackled by gene therapy.

There is a worry among those active in this field that the public needs reassuring that gene therapy is not concerned with creating Frankenstein monsters or the type of eugenics[5] associated with Nazi Germany. Whilst such anxieties are probably unjustified, in any area such as this where fears are widespread and the information limited, there needs to be public debate and education to put the objective facts into perspective.

Perhaps the greatest influence on the incidence of genetic disease will have little to do with medical advance or scientific progress. Dr Steve Jones in his aforementioned Reith Lectures stated that, 'there has been a drop in inbreeding in human populations in the recent evolutionary past. An increase in mating outside the group is one of

4 This list indicates the principal current targets for gene therapy efforts and is not meant to be complete. Many of the diseases listed can be caused by defects in more than one gene; the gene defect listed is the defect targeted by current research.

5 A form of eugenics was practised in the USA in the inter-war period. Some 30 states passed laws requiring the compulsory sterilization of certain groups of individuals. For example, the 'feeble-minded', epileptic, and mentally ill. The legislation was never comprehensively enforced but nevertheless many thousands were compulsorily sterilized, mostly in California.

the most dramatic changes in recent evolutionary history. Its effects may outweigh anything medical genetics is likely to be able to do'. The argument is that increased geographical mobility will have a genetic effect as large numbers of children will be born to parents who are now less likely to be related – the increasing distance in the birth places of couples would indicate this – and thus are less likely to carry copies of the same defective gene. Jones postulates that we may be entering a time of genetic well-being because the harmful genes will be partnered by a normal copy thus preventing manifestation of many autosomal recessive diseases.

Since genetics and gene therapy are certain to be areas of increasing medical importance it has been proposed that 'there must surely be a common core of knowledge which every graduate should possess' (Johnston, 1992). The Royal College of Physicians of London (1990) published a core curriculum and it is expected that the report will be taken up by the General Medical Council and the medical schools. Johnston suggests that the teaching should cover, as a minimum, precision in diagnosis, counselling, molecular genetics and the application to the specialty involved. If such a policy is adopted the increasing demand for genetic counselling should be met by an increased number of trained specialists in this area.

THE EPIDEMIOLOGY OF GENETIC DISEASE

The prevalence of genetic disease is estimated to be between 38 and 51 per 1,000 population (Kingston, 1989). Congenital malformations make up the largest proportion of this total with chromosomal abnormalities, autosomal dominant and common disorders with an appreciable genetic element also being relatively frequent. Less common are autosomal recessive and X-linked recessive disorders.

Cystic fibrosis (CF) is the most frequent lethal autosomal recessively inherited genetic disease among the Caucasian population. It has an incidence of about 1 in 1,600 live births. Boys and girls have an equal chance of being affected. Around 450 CF babies are born each year in the UK (Goodchild and Dodge, 1985).

One of the more common X linked recessively inherited disorders is Duchenne muscular dystrophy. It has an incidence of 1 in 3,500 males at birth. Boys are usually confined to a wheelchair by the age of 11 and dead by 25. Some female relatives have clinical evidence of disease and there is a potentially high risk to close relatives. Becker muscular dystrophy is less severe and has an incidence of at least 1 in 20,000 males at birth.

Ethnicity is an important risk factor for genetic disease. Ashkenazic Jews, for example, are particularly susceptible to Tay-Sachs disease. The disease has an incidence of about 1 in 3,600 Ashkenazic Jews with a carrier frequency at least ten times as high as in non-Jews (1 in 22-30 against 1 in 300, Garver and Marchese 1986). Other diseases associated with Jewish ancestry include adult Gaucher's disease and Niemann-Pick disease.

Sickle-cell disease is relatively common among blacks. Sickle-cell trait (ie. a carrier of the disease gene) is found in about 1 in 10 black Americans. Sickle-cell anaemia (the disease itself) occurs in around 1 in 400 black Americans. It is autosomally recessively inherited. There are about 6,000 people with the disease in Britain (Brozovic, 1992). Mediterraneans have a tendency towards Beta Thalassaemia and Orientals towards Alpha Thalassaemia (Garver and Marchese, 1986). Thus, ethnicity should be considered since risks are increased for certain inherited diseases among particular ethnic groups to levels significantly above the overall population incidence.

The numbers of those affected by inherited disease can range widely depending on what criteria one uses. For example, if conditions such as coronary heart disease were included, in which there appears to be a considerable genetic element but by no means are all such cases explained by familial predisposition, the figures

could be very high indeed. The British Colombian Department of Health (Canada) has suggested that 5.5 per cent of the population will develop a genetic disease by the age of 25 and some 60 per cent during their lifetime, if one includes predisposition to common disorders (RCP, 1991).

Red-green colour blindness is determined by a recessive gene on the X chromosome. Unaffected women are often carriers; its effects in women are masked by a dominant gene conferring normal colour vision (a similar mechanism prevents haemophilia and Duchennne muscular dystrophy manifesting in carrier females). Colour blindness is not classed as a disease in this paper, but if it were it would be the most common X-linked condition.

'Pharmacogenetic disorders', as defined by Vogel (1959), refers to hereditary disorders revealed solely by the use of medicines. However, more recently a wider definition of the term has been adopted so that 'it now embraces all genetic contributions to the considerable variation that exists between man and pharmacological agents that he uses' (Griffin, 1986). Malignant hyperpyrexia (hyperthermia) is a rare pharmacogenetic disease with an autosomal dominant mode of inheritance. Any inhalational anaesthetic or skeletal muscle relaxant given to susceptible individuals induces fever, rigidity, hyperventilation, cyanosis hypoxia, respiratory and metabolic acidosis, hyperphosphataemia with a raised glucose. The mortality of the condition is high at 60-70 per cent (Griffin, 1986). A further example of pharmacogenetic disease concerns the porphyrias group of disorders which have many different symptoms. In acute porphyria severe attacks of colicky abdominal pain, vomiting, constipation and psychiatric disturbances are present. It is an autosomally inherited disease but with varying degrees of penetrance. The disease may be entirely symptomless or dormant and aroused only by the consumption of medicines such as barbiturates. 'There is no evidence that an acute attack of porphyria can be precipitated by drugs in the absence of genetic disposition' (Fletcher, Griffin 1986).

If a narrow definition of genetic disease were adopted, for example, only diseases with clear evidence of genetic contribution which lead to premature death (for our purposes say prior to the age of 60) the numbers involved would clearly be much smaller.

GENETIC COUNSELLING IN PRACTICE

Harris and Hopkins (1991) argue that 'genetics may be a powerful instrument for prevention but the primary goal is informed choice without coercion'. The Royal College of Physicians (1989) suggest that three core ethical principles should underpin genetic counselling in practice. Firstly, the autonomy of the individual or the couple; secondly, their right to full and complete information; and finally, the preservation of the highest standard of confidentiality.

Other guidelines for genetic counselling have been proposed. For example, it has been argued that those counselled should recognise that there are only specific diseases and specific modes of inheritance and this point should be emphasised to counselled clients; there is no such thing as a non-specific liability. Another basic principle is that those counselled deserve counselling based on the best and newest information on offer since the consequences can be so far-reaching. The type of risk as well as the chances of occurrence should be stressed, since the less severe the potential defect the greater the risk parents will be willing to take.

Clarke (1991) argues that 'ostensibly non-directive counselling in connection with prenatal diagnosis is a sham, not because of a personal failure on the part of the genetic counsellor but as a direct result of the structure of the encounter between counsellor and client'. He continues that if prevention of genetic disease is an explicit goal, although he maintains that it should not be, then the non-directive nature of genetic counselling is immediately abandoned 'in favour of a genetic public health policy, or eugenics'. Clarke claims that one cannot maintain a non-directive approach to counselling whilst simultaneously aiming to prevent that disorder, he 'contends that an offer of prenatal diagnosis implies a recommendation to accept that offer, which in turn entails a tacit recommendation to terminate a pregnancy if it is found to show any abnormality'. Non-directive counselling is, in his opinion, unattainable since merely the offer and acceptance of genetic counselling has set up a likely chain of events in everyone's minds. However, there are those who opt for a prenatal diagnostic test with no intention of termination even if the fetus is found to be abnormal. Such parents may feel that they could prepare practically or psychologically for the birth of an affected child better with the knowledge provided by prenatal diagnosis. Thus, not everyone will agree with Clarke's attitude.

The actual process of genetic screening can be remarkably simple, for example, with regard to cystic fibrosis (CF) a rudimentary mouth

wash obtains enough buccal cells to provide DNA for testing for all four major mutations which can individually lead to CF. These four mutations account for 80-85 per cent of CF carriers in the indigenous British population, however, only 50-60 per cent of southern Europeans or Jews will be identified since there are important genetic differences. The 15 or so per cent of CF carriers not identified in the British population will be accounted for by over 150 different mutations. The BMA (1992) have said that at current levels of detection, even with a comprehensive screening programme, 29 per cent of CF couples would slip through the net. However, this fact should not blur the enormous benefit that may result to the 71 per cent identified.

In the past, lack of public and professional knowledge concerning genetics has led to disasters in screening programmes. In the USA sickle cell disease became a political issue in the 1970s. At that time carrier identification was available but prenatal diagnosis was not, so no reproductive options apart from not having children at all were offered. About a dozen states passed laws to require black people to take compulsory testing. An inadequately educated profession and public held a widespread misconception that sickle cell trait was actually the disease state; rather than indicating carrier status. Many carriers themselves thought that they had the disease. The need for genetic counselling services and for protecting the confidentiality of test results were ignored. Carriers were subsequently stigmatized and had difficulty in obtaining health insurance and jobs. Many black Americans felt that the screening was merely a devious way to discourage black people from having children.

The need for confidentiality with regard to medical records is a matter that patients and doctors assume is not for debate. This presents particular problems for clinical genetics which requires information about entire families before accurate advice can be given. Johnston (1992) points out that 'at a genetic clinic, intrafamilial problems such as non-paternity may be revealed or concealed. A promise given by the clinician to respect such a confidence can cause difficulties when more than one family member seeks advice'. Patients must feel able to entrust their doctors with sensitive details, in order that the doctor can give accurate information to other family members whilst not disclosing their patients' secret.

Genetic counselling can be potentially harmful as well as beneficial; the King's Fund consensus statement (1987) points out several possible positive and negative consequences of screening programmes. Examples of benefits include the provision of authoritative information, relief from uncertainty, support during a

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BOX 4 Genetic counselling: Case studies

Case 1: A 25-year-old university graduate requests counselling concerning himself and his fiancee. His fiancee's parents became concerned when they realised that the man had two half-sisters who were badly malformed with Hurler's syndrome. They felt that potential offspring from this union may be similarly affected, and indeed two doctors advised against the marriage on the grounds of grave risk to any children. The man decided to turn to family genetic counselling to obtain a more professional opinion regarding the risks to any offspring they may have.

Hurler's disease is known to be autosomal recessive, meaning that for the disease to manifest itself a person must be homozygous for the defective allele in question. The defective gene must be carried on two homologous chromosomes, one contributed by the mother the other by the father. Thus, both parents must carry the defective gene for their children to be at risk of manifesting the disease. Since neither of this man's parent's manifests the disease, each possesses at most one defective gene (ie. heterozygous). Every child of carrier parents has a 25 per cent chance of being homozygous for the defective gene and thus manifesting the disease, a 50 per cent chance of being heterozygous and thus personally unaffected (although a carrier of the defective gene), and a 25 per cent chance of being homozygous for the normal allele.

The man in question cannot be homozygous for the defective gene since he does not personally suffer from the disease. Further he has a different mother to the affected siblings, and whilst his father must be heterozygous for the defective gene, his mother, since this is a rare condition, is probably not. The man has a 50 per cent chance of being a heterozygous carrier. The fiancee can be assumed to have a normal risk for being a Hurler's syndrome carrier. The probability that both the man and his fiancee are heterozygous carriers is as follows:

0.5 (man) x 0.006 (fiancee) = 0.003 or about 3:1,000

Even if both parents were carriers the chances of a child manifesting the anomaly is 25 per cent giving an overall risk for future children of: 0.25 x 0.003 = < 1:1,000. Whilst this is a rather rough and ready estimate it does clearly demonstrate that no reservations towards this marriage should be made on the grounds of a risk of genetic disease; especially when one considers that 2-3 per cent of children are born with some type of congenital malformation or hereditary disease.

Case 2: A healthy brother of a phenylketonuria patient wishes to marry but wants to know the risks to any children they may have. There is a two thirds probability that the proband inherited the gene from one of his parents. The chances that he and his wife are both heterozygous is about one in 75. Should both parents be heterozygous there is a one in four risk that their children will be homozygous for the defective gene. The combined probability of an affected child is $1/75 \times 1/4 = 1/300$. The likelihood of an affected child is thus little different to the chances of a child acquiring some form of genetic disease in the general population.

Source: Fuhrman, Vogel (1983).

period of crisis, and the expansion of the individual's scope concerning choice. The potential harms include worrying delays whilst confirmatory tests are conducted, the distress that may ensue from false positive results, and the erroneous reassurance that may follow false negative results.

Frets et al (1990) looked into factors influencing reproductive decision making after genetic counselling. The study was based on 164 couples who sought genetic counselling at the Department of Clinical Genetics at the University Hospital of Rotterdam, Netherlands. The study took place two to three years after the counselling to establish the client's subsequent reproductive choice. Three levels of genetic risk were identified. A low risk category of less than a five per cent chance of having an affected child; an intermediate category with a 5-15 per cent chance and a high risk category with a risk of over 15 per cent. Over 90 per cent of the sample were referred because they had an affected relative and about one-third of these had an affected child.

All the couples in the study not personally acquainted with the disease (ie. no close relatives such as parents, children or siblings had the disease) opted for having children. All those at risk of a disease causing early death (2-6 months) also opted for having children. Nearly all of the couples who either had no living children or had an affected relative (not a child) opted for having children, whereas about one in four of those with an affected child opted for having no further children. Nevertheless over two-thirds of those with a high risk and those interpreting their risk as high decided to have children. The largest group refraining from having children were in those cases where the disorder was a chronic physically incapacitating illness, but even here less than one in three declined further children.

In general the decision-making process will take into account a number of factors. For example, where there was a low genetic risk (less than five per cent) and the couple had no children 100 per cent of the couples wanted future children. Where there was a high genetic risk (over 15 per cent) and the disorder was a severe disease 72 per cent opted for having children but this figure decreased to 47 per cent when combined with the unavailability of prenatal diagnosis.

Frets' study also demonstrated that perceived and actual risks were not always the same. Eighteen per cent of couples in category one and thirty-five per cent of couples in category two interpreted their risk as high; and twenty-three per cent of couples in category three interpreted their risk as low.

Fret et al concluded that the apparent disregard for the consequences of the risks (eg. 72 per cent of those interpreting the risk as high and the disorder as severe decided to have children) may reflect an unconscious reaction to the 'unbearable' feeling of lowered self-esteem owing to the hereditary nature of the disease. A further

point which the study shows is that couples at risk for a disease leading to early death were more prepared to take the risk than those at risk for a prolonged illness. Four fifths of the couples said that they had benefitted from genetic counselling and that it had helped them to make an informed decision.

Genetic counselling facilities

The results of a survey reported by the Royal College of Physicians (RCP) of London (1991) claim that there were 165 'Whole Time Equivalents (WTE)' clinical staff employed in all grades medical and non-medical associated with genetic centres in the UK. The geographic distribution of staff is very uneven ranging from 6.28 WTE per million population in Wales to 1.25 per million population in Mersey. There were 125 medical staff in British genetic centres and consultant clinical geneticists comprised the single largest group. Twenty-three genetic centres were in existence at the time of the survey. This emphasises the inadequate provision of genetic services in Britain and why only a small proportion of those who need advise actually receive it. Most patients depend on the primary health care team to answer their questions on risks of recurrence.

Clinical genetics is largely an out-patient speciality. Diagnostic problems and genetic counselling are the main clinical activities. The RCP argue that genetic counselling should be regarded as a procedure comparable to a surgical operation with the potential to heal and to harm when the consequences may extend through several generations.

There should, argues the RCP, be more commitment towards undergraduate and postgraduate education in genetics because of the rapidity of new developments against a background of poorly taught genetics at medical schools. A genetic family register should be held by genetics centres to support families and to enable families to be told about new advances. Regional organisation of genetics centres with close integration of clinical, cytogenetic and molecular laboratory genetics would help facilitate this objective.

New molecular technologies bringing improvements in diagnosis and management of all genetic and chromosomal disorders cannot be exploited properly without appropriately trained personnel. The present establishment is inadequate for current needs according to the RCP and furthermore the demand for accurate and empathic genetic counselling is expected to increase exponentially as unsuspecting individuals and their relatives are found to be carriers in population screening programmes.

Summary

Genetic counselling must follow certain ethical and moral guidelines if it is to be acceptable in practice. Confidentiality must be maintained and those counselled should be left to make any difficult decisions themselves after being provided with complete and up-to-date information. Genetic counselling should follow a non-directive path, even if this is a difficult policy to achieve completely in practice, as the counsellor may misinterpret the moral, ethical and religious beliefs of those counselled if they attempt to encourage a particular course of action.

For the knowledge gained in the area of hereditary disease and genetics to be exploited fully more facilities for counselling and genetic testing will be required. If the public and medical profession are made more aware of the possibilities that this field of medicine holds perhaps greater use will be made of existing facilities necessitating the emergence of a further expansion of genetic counselling units.

The case studies in Box 4 provide an example of the need for professional genetic counselling as risks can be greatly misconstrued by simply relying on 'common sense' pronouncements or even those of the medical profession who are not knowledgeable concerning this field of expertise.

PSYCHOLOGICAL, PERSONAL AND ETHICAL ISSUES

Genetic counselling is not merely concerned with scientific problems, it must deal with psychological, social and ethical ones as well. In the past it was a special conscious decision not to have children; now a couple can easily decide whether or not to have children. This decision should include a consideration of genetic risks. It is important for the geneticists, who will often counsel every day, to be aware in their daily routine that for most of their client's such counselling is a rare, perhaps once-in-a-lifetime experience, coloured with anxious expectations and intense emotional stress.

Information, even if it is negative, is meant to be effective and may affect a couple's, or individual's, entire way of life or completely alter their future expectations. It may even drastically alter a particular relationship. The information that one spouse is a carrier can easily lead to a massive guilt complex. Thus, it must be stressed that there is no personal responsibility; in the same way that a new mutation is an accident, no-one has any choice about the genes which they inherit.

However, genetic counselling should be a mostly pleasurable task, a chance to allay anxiety, reduce fear, and to reassure. Seldom will it be necessary urgently to warn a couple and confront them with a very difficult and painful decision. The overall effect is to encourage couples to start a family.

Every completed counselling session should be followed-up with a letter sent to the family setting out the relevant details since even if the information was properly understood it will pale with time. Indeed if the information went against the couples wishes and desires over time the information may gradually fall more favourably into line with their ideal outcome rather than represent the true objective facts (Fuhrman and Vogel, 1983).

With regard to the issue of objectivity, neutrality and non-directive counselling, Fuhrman and Vogel (1983) argue that 'there is no such thing as being totally objective. The manner in which the facts are presented alone will influence the decision, and the presentation is unavoidably subjective.... We do not believe that it is either right or desirable to evade a personal commitment'. They add that 'the patient's personal disposition, philosophy, and religious convictions must be considered as well as scientific facts'. Whilst the counsellor may be unable to produce totally impartial advice this is no reason to recommend a particular course of action be made by the counsellor. In attempting to make a personal commitment as Fuhrman and Vogel suggest the counsellor may, for example, misinterpret the personal

disposition or philosophy of the client. It may be more advisable to try to be non-directive, neutral and detached as possible whilst recognising that this is unlikely to be achieved in full. Actively to encourage the inherent biases in counselling may not be a particularly desirable aim, indeed many would probably see the minimisation of these biases as more desirable.

Psychological and personal consequences of abortion

Prenatal diagnosis presents considerable problems without offering any ready-made solutions. If abnormalities are found the woman is likely to opt for an abortion but this should not be taken for granted, it is her choice and she will have to live with it. Vogel and Fuhrman (1983) say that every experienced counsellor, for example, will know of women who have chosen to have a child with Down's syndrome. More desirable than abortion must be the avoidance of high risk pregnancies.

Of course, if a woman chooses not to abort an abnormal fetus the consequences can be devastating; she may have a life-long dependent in need of constant attention and/or medication. It is a difficult decision to make but one that needs careful consideration of the future implications for the family, the affected individual and those who come into contact with them.

The issue of genetic counselling and prenatal diagnosis is a particularly emotive one when society encompasses such diverse movements as 'prolife' and 'prochoice'. These groups represent opposite views on abortion and motherhood. Among the moral guidelines of many societies are those to be truthful, to avoid inflicting harm on others, to respect suffering, and to be fair. If these goals have all been internalized, moral conflict over choices or counselling about prenatal diagnosis is almost inevitable. Whilst abortion kills a fetus it is argued this fact is masked by using terms such as 'selective', 'therapeutic' or referring to abortion as a 'termination of pregnancy'. Of course, on the other hand, not aborting may have serious adverse life consequences for the mother, the family, the affected individual and society.

The long-term effects of guilt and depression after abortion must also be considered. Leschot (1982) suggested that the difficulties in accepting therapeutic abortion were to some degree comparable with the process of accepting a malformed child at term. The decision to terminate a second trimester pregnancy due to a malformed infant is an event with long-term negative side-effects for most patients' and their families. Once the decision to terminate has been taken, the

counselling process does not stop and the counsellor must appreciate that he has a responsibility to support the couple in their decision and not to reinforce doubts. Thus, prevention of the birth of a malformed child is by no means a panacea. There are, however, some women who appear to suffer relatively little after having an abortion but these are probably the minority.

Psychological effects of being a 'carrier'

Massarik (1981) looked into the question of whether there is a stigma attached to being a disease carrier. He claims that one in five carriers report being 'deeply troubled' about the matter and a further 30 per cent say they are 'quite concerned'. Independent interviews carried out with spouses suggest that typically the carrier felt more concerned about being a carrier than their spouses imagined that they would have been. However, it does appear that the initial impact of being a carrier is absorbed as time passes and concern (or anxiety) levels further decrease. One year after diagnosis as a carrier no-one in the survey Massarik refers to were 'deeply troubled' and only 15 per cent were 'quite concerned'.

Insurance and Genetics

Any emotive subject such as genetic counselling, and its implications, will generate many practical, ethical and moral dilemmas. On the surface it may seem only natural to endorse Warnock (1992) who says 'to attempt to ensure the birth of a healthy baby seems to be morally a wholly admirable aim'. But as soon as one begins to delve a little deeper into this issue a whole host of potential problems arise; indeed Warnock is aware of the fear that some people may have of a 'slippery slope' with genetic techniques being used for reasons other than scientific or medical benefit. The Glasgow based 'Herald' had an engaging discussion between the Editor (Arnold Kemp) and Medical Correspondent (Alan MacDermid) and Dr Angus Ford and Dr Vivienne Nathanson, Chairman and Secretary of the BMA's Scottish Council respectively, in April 1992 which raised several interesting aspects of this debate. Initially 'The Herald' advanced the notion that genetic mapping may allow doctors to predict genetic-linked diseases in individuals which could mean the end of risk-sharing in life insurance policies, however undesirable a move away from 'pooling' of risks may be, since many people will be able to know what life threatening ailments they are likely to suffer from in future years. Dr Nathanson added that the state may not be prepared to fund the education and companies may be unwilling to employ people,

especially where long periods of training are required, if they are likely to die or become disabled in the near future from a previously identified genetic abnormality. Dr Nathanson firmly believed that information concerning genetic make-up should be kept exclusively between doctor and patient. She predicted that it will be another 20 years before anything sophisticated can be done with gene mapping which she says 'gives us time, but we have to start thinking about the state limiting the freedom of employers, insurers and so on to demand information'.

Insurance companies, however, justifiably fear that people at risk might have a genetic test early in life and finding themselves positive take out a large amount of life cover, or living assurance, without revealing the results of the test. In the USA insurance companies are considering introducing 'super select' categories with reduced premiums for those prepared to undergo a series of genetic tests – providing, of course, that they test negative.

Buckingham (1992) writing in the Guardian says that 'so far Britain's insurance industry shows all the signs of repeating the morally inept and socially dangerous approach it initially adopted towards HIV testing'. A European Parliament resolution has said insurers should have no right to demand genetic testing as a requirement for issuing a policy, nor should they be able to require the disclosure of any other genetic information. Further, insurers should not be able to inquire about previously performed tests as a condition for cover. The Association of the British Insurers has expressed a willingness to confront such legislation if it were adopted here.

General ethical issues

The aforementioned 'Herald' interview included an important issue concerning the termination of pregnancy after prenatal diagnosis. Suppose motor neurone disease could be antenatally diagnosed – a disease which may not cause death until one is 60 or more – is it moral or ethical to terminate a pregnancy for something so many years ahead? Indeed would people really want to know that they are likely, ultimately, to die from motor neurone disease? It is also likely that some of those at risk of motor neurone disease will die of something quite unrelated to the disease before it becomes evident. Indeed a cure may be found during the lifetime of a potential motor neurone sufferer.

On a more flippant note Dr Ford wondered whether we will begin to see marriage contracts that say 'I have had my genotype properly mapped out and I am not a carrier of cystic fibrosis'. We may, he suggested, see the emergence of a sort of selective breeding system;

Lonely Hearts Columns may have messages like 'Attractive brunette, Cystic Fibrosis carrier, seeks non-carrier partner'. Taking this one stage further 'The Herald' asks whether we might, one day, need a licence to bear children. In the same way one is required to take a test before being allowed to drive a car, a test may be required before one is deemed suitably able to give birth – this suggestion belongs perhaps more in the realms of fantasy than fact.

The voice of church has not been silent on this subject, John Habgood, the Archbishop of York, writing in the 'Times' claims that 'pressures on women in the US to undergo foetal testing are now so strong that those who refuse are made to feel morally irresponsible'. He continues 'it is a platitude to say that scientific and technical advances can be used for good or bad ends. The difficult bit is deciding which is which.' Habgood urges a vigorous, wide-ranging and well-informed debate on the subject in the UK.

Culliton (1991) says that 'the discussion of ethical issues has, for the present, something of an abstract air about it. But that will not last. Once gene therapy is a real, practical part of medicine, the imaginary fears will probably evaporate, and the other issues will have to be faced just like any others in medicine'. Hopefully clear guidelines about case selection for treatment, and apportioning cost burdens can be established before rather than after gene therapy becomes a practical procedure.

Early advocates of prenatal diagnosis advised a policy of withholding the procedure from parents who refused to abort in the event of positive findings. The rationale behind this was that scarce resources should only be used for those willing to abort and also that enduring unknown risks should only be borne by those not willing to abort. Prenatal diagnosis was said to serve no purpose unless termination was a viable option. However, this position did not go unchallenged. It was argued that, depending on the disorder, families could usefully prepare for the birth of an affected child with the aid of prenatal diagnosis. However, in practice, almost all of those who cannot accept abortion decline the risk of amniocentesis.

Clarke (1991) argues that prenatal diagnostic programmes may affect society as a whole, with long-term repercussions for the status of, and provision for, the mentally and physically handicapped. He believes such effects should be studied in order to evaluate programmes effectively. Warnock (1992) argues that 'intervention of a preventive nature is, so far, aimed at the abolition of a few disastrous diseases which have a fatal outcome or cause an intolerable burden to the sufferer. To try to prevent the birth of children with such diseases is not to imply any general thoughts about the handicapped, many of

whom undoubtedly lead tolerable and indeed enjoyable lives and for whom undoubtedly more could be done to make their lives better'. The same, she suggests, cannot be said for those with Duchenne muscular dystrophy or Cystic Fibrosis (CF) and thus the mildly handicapped should not speak on behalf of these children. However, another issue is raised here. Progress in heart-lung transplantation (the largest single group of transplantees are CF sufferers) as well as more advanced routine therapy means that even now a CF sufferer may live a relatively long and tolerable life. Fifty years ago 80 per cent of CF sufferers would not have lived beyond one year. 'Although a median expectation of life of 20-25 years are usually cited ... these figures are for a birth cohort of 20-25 years ago, when treatment was less effective, and they suggest that most patients born with CF today would expect to live well into middle age, working and living independently' (Editorial, Lancet 1992). In the future progress in gene therapy may lead to a cure for the individual with CF. Thus, to terminate a pregnancy where CF has been diagnosed in the fetus may, certainly for those who foresee significant advances in the near future, be a rather short-sighted decision. A parent who terminated such a child just a few years before a major breakthrough in CF treatment may find that decision very difficult to live with. On the other hand it may be that the future for CF sufferers is not as optimistic as all that and a termination may, even in retrospect, appear to be the correct decision to many parents who undertook such action.

Another point that Clarke raises concerns the fact that most fetuses with Turner's syndrome if not diagnosed would either abort spontaneously (in over 95 per cent of cases (Kingston, 1989)) or result in the birth of a healthy girl likely to live a rewarding and independent life. In some infants the only detectable sign is lymphoedema[6] of the hands and feet; the most consistent features are short stature and infertility. Intelligence is within the normal range and a modest increase in growth can be stimulated by growth hormone therapy. Oestrogen replacement treatment is necessary for pubertal development and fertility can be achieved by ovum donation. Those cases that are diagnosed at amniocentesis, usually carried out because of advanced maternal age, tend to be terminated by couples often older than average who may desperately want a child but when told they have an abnormal fetus may not recognise that Turner's syndrome does not cause mental retardation and rarely causes severe medical problems. However, it appears that the mere fact that parents

6 Lymphoedema means dropsical swelling of a part or organ due to obstruction to the lymph-vessels draining it.

are told that they carry an abnormal fetus usually leads to an abortion since they are often unwilling to give birth to an abnormal chld even if the abnormality is treatable.

Pembrey (1991) says that most parents can reconcile the apparent inconsistency of love and protection of a handicapped child whilst deliberately avoiding the birth of a second. However, he suggests that few would be unaware that selective abortion throws into doubt the value of the life of their handicapped child. Indeed Simms (1991) suggests that with the benefit of hindsight many parents who have experienced the emotional drain and bitterness associated with the unsought task of caring for a handicapped person for many years would have had an abortion if they had realised what awaited them. Of course, some parents may argue the reverse, feeling great satisfaction in bringing up a handicapped child.

An issue encompassing both economics and ethics concerns cases in which a prospective mother is told that her offspring is 'genetically abnormal' but refuses abortion and subsequently gives birth to a defective child. Some may argue that society should not be responsible for the health care costs associated with caring for this child and that the mother should be held accountable for her decision. However, equally vigorous support for the mother may emanate from those defending a mother's right to decide whether or not to have her child, and ihdeed some may argue that the child has a right to life.

Patenting and research in genetics

Since the discussion of systematic mapping of the human genome began in 1985, there have been concerns expressed about property rights to the data. The issue of patenting of such information is currently posing a threat to progress in human genetics. Concern has been voiced by those anxious regarding putting large sums of money into the genome project only to see other countries walk away with the data completely free and then exploit it commercially (Galloway 1992).

In August of 1991 the Human Genome Mapping Project in London generally agreed that steps should be taken towards data sharing and that groups should screen each others data for overlap. However, the US National Institutes of Health (NIH) had already filed patents en masse for the first 337 Venter cDNA sequences and proposed thereafter to patent them 1,000 at a time. Walter Bodmer, president of the Human Genome Organisation (HUGO), writing in the Guardian (April 1992), says that geneticists, scientific organisations and governments around the world are uniting in opposing American attempts to patent small fragments of the human genes without knowing what they actually do in the body. Indeed even in the US

there was considerable unease at this type of patenting both from individual scientists and the Department of Energy and the Office of Genome Research. The UK's position was that small fragments of cDNA should not be patented. However, complete gene sequences, such as the successful patent application for the Cystic Fibrosis gene, should be patented.

One of HUGO's main aims is to ease the exchange of data and material and to encourage the spread of essential technologies. HUGO's view is that all the basic genome data should be freely available all over the world. Bodmer agrees that 'patenting to protect intellectual property is essential for the commercial exploitation of the discoveries that come from human genome analysis which I am sure will underpin the pharmaceutical industry of the future'.

The problem in the UK surrounding patents concerns the fact that disclosure would undermine a patent application. Thus the information must be kept secret, and therefore unpublished, until a patent is granted. However, as the BMA (1992) says, 'the failure to reveal results at the earliest possible moment would be directly disadvantageous to potential patients, and therefore to public health'.

The crux of the matter is not whether but at what stage to patent without inhibiting the international collaboration and exchange of materials and data essential to the success of the project. There is no need to patent the DNA sequence itself leaving this information to be exchanged freely among the scientific community. Patenting of gene fragments could seriously inhibit the exchange of information and materials at a premature stage. However, while recognising the importance of the protection of industrial property rights for the development of valuable medicines, Bodmer concludes that 'most important of all is that the enormous value of the project to the future health of mankind must not be diminished in any way by wranglings over patents'. Galloway concludes that the group at NIH are becoming increasingly isolated and embattled.

Medicolegal Aspects

'In North America at least, prospective parents.... have been quick to enlist the aid of the legal profession when the chance to avoid a serious congenital defect has been missed' (Milunsky, 1986). Indeed Shaw (1986) says that there are an increasing number of malpractice suits being enacted called 'wrongful birth' or 'wrongful life'. Many of these claims are based on the parents argument that they were unable to make an informed decision concerning reproductive choices due to a physicians negligence in terms of lack of information or inaccurate   **31**

information. The distinction between 'wrongful birth' and 'wrongful life' lies in the fact that in one action is brought by the parents and in the other by the child. In cases of 'wrongful birth' the parents claim that they have been wronged because the birth of their abnormal child could have been avoided except for a physician's negligence. In cases of 'wrongful life' the child claims that he/she should not have been born and would not then have endured the pain, suffering and misery that they feel has spoiled their life.

'Wrongful birth' suits originated from action brought by parents regarding unwanted children due to a failed sterilization procedure, however, judges viewed the 'blessing of a cherished child' to far outweigh any other considerations. Gradually compensation began to be paid in cases where the child was defective. 'Wrongful life' suits brought by children have been far less successful than parental suits.

In addition it has been suggested that unwanted or unplanned normal healthy children should, when resulting from a failed vasectomy or abortion for example, be called 'wrongful conception' or 'wrongful pregnancy'. When a healthy child claims that they should not have been born the suit should be called 'dissatisfied life' (such cases usually result from complaints of stigmatization due to illegitimate status).

Summary

Genetic counselling encompasses a wide range of issues and involves far more than merely stating the arithmetical risks of inherited disease to future offspring. Psychological, social and ethical considerations must also be given attention. A child with a serious medical condition can be a burden and can make life stressful and mentally and physically draining. However, aborting a potentially abnormal child can lead to guilt and depression and may disrupt some people's lives to a similar degree, if in rather different ways, to that experienced with an abnormal child.

In response to some of the ethical issues raised Warnock (1992) claims that certainty can only be produced by legislation 'and it is for this reason that I believe legislation may well be required in some areas of possible human genetic manipulation. For the difference between the non-criminal and the criminal.... is at least clearer and more definite than the difference between right and wrong'.

Genetic counsellor's must be sensitive towards those counselled on giving news that they are a carrier for some particular disease. This can be a very unexpected and traumatic event with considerable practical and psychological consequences.

The issue of insurance and known genetic risks needs to be made clear before technology reaches a state to necessitate guidelines on this issue. It is important that the present uncertainty surrounding life insurance and genetic disease is resolved before a position is reached which could be problematic if the current situation still prevails.

The status and provision for the handicapped in society remains an important concern. Some people have postulated that with the potential for fewer abnormal births the handicapped will become an ever smaller and more stigmatised group – with the majority of births leading to 'near perfect' (in terms of health) children. On the other hand the fact that fewer people may be handicapped in the future may mean more resources can be devoted to those who are handicapped enabling them to live more enjoyable and comfortable lives. Only time will tell which of these scenario's is closest to the truth.

For some inherited diseases, such as possibly CF, a cure may be not be too far away in which case fetuses with this disease need not be aborted. Indeed for many conditions improved therapy and disease management may mean that a decent length and quality of life can be enjoyed. As medical science progresses there may be less and less need for termination as more and illnesses can be effectively managed or cured.

With regard to patents a consensus appears to be growing suggesting that only complete gene sequences should be patented and not gene fragments – which should be widely available to those researching in this field. Legal suits brought against doctors may increase although this country has not yet shown such a propensity to sue the medical profession as the North Americans have.

ECONOMIC ASPECTS

Whilst this report attempts to be broad based and wide ranging, and thus has many varied and potentially far-reaching economic implications, the main body of economic evidence which is available relates primarily to individual screening programmes. It is therefore necessary to restrict the economic analysis to rather more narrow consideration than has previously been the case.

An economic evaluation of a genetic screening programme for Tay-Sachs disease was undertaken by Nelson, Swint and Caskey (1978). They saw the averted costs of hospitalization of Tay-Sachs babies as the main benefit against which both direct (labour costs, use of personnel facilities and materials, and educational material) and indirect (travel costs and waiting time) screening costs must be weighed. It was assumed that a fetus would be aborted if identified with Tay-Sachs disease. The costs of amniocentesis and abortion were assumed to be the same as the costs of delivery and were therefore omitted from the analysis. Even with a conservative estimate of the benefits, the programme benefits outweighed the costs by at least two to one. With high estimated benefits the programme benefits to costs ratio was reported to be over six to one. The authors stress that their results only apply to a high risk population nevertheless the programme was justified on the basis of tangible benefits and the existence of other benefits is, they claim, likely to reinforce the positive result. However, psychological costs associated with abortion should also be considered.

Other screening programmes have also been economically appraised such as Veale's 1980 study of screening for phenylketonuria where he defined costs as including initial equipment, collecting specimens, running expenses and investigations, and in providing 10 years treatment at home. The benefits consisted of averting the costs of caring for handicapped children and the recovery of potentially productive members of society. He concluded that screening for phenylketonuria was worthwhile in economic terms. Henderson (1982) considered the benefits of maternal serum AFP screening for Open Spina Bifida. The paper assessed the tangible benefits to society from changes in consumption and output resulting from the prevention of spina bifida births and replacement with normal births. Intangible benefits which parents derive from children were also estimated. The benefits were seen in terms of comparing the net costs associated with a cohort of handicapped children to society born in the absence of screening with that of a replacement cohort of normal children. The benefit was decreased as the replacement ratio

increased. However, if a parent experienced a loss of psychological benefit through having a spina bifida child the benefit of screening was increased. For a cohort of 100 prevented births with a 100 per cent replacement ratio the benefit was between £1.1 million and £1.9 million. The estimated cost of averting these births was £0.3 million. Henderson concluded that the tangible benefits outweighed the tangible costs by about £1 million per 100 births averted per year. The prevention of subsequent births to parents with affected children was not considered as a benefit of the programme as they would normally be subject to prenatal testing.

A more general appraisal of screening programmes was undertaken by Layde et al (1979) when they carried out their cost-benefit analysis of maternal serum alpha-fetoprotein screening. The evaluation was based on screening plus abortion costs of affected fetuses against providing care for live-born infants with defects. The costs were those incurred in mounting the programme which included maternal serum alpha-fetoprotein screening coupled with ultrasonography and amniocentesis where indicated. The benefits were the averted costs of institutionalisation and medical care for the children born with defects and lost parental income averted. The authors acknowledged that there were many intangible costs and benefits which were not included. The costs and benefits were estimated for a theoretical 100,000 pregnant women at risk in two situations. Firstly, where the pregnancy is 'replaced' and secondly, where it is not 'replaced'. The true situation they suggest lies somewhere between the two. They estimated the total economic benefits roughly as double the total costs of screening 100,000 pregnant women.

Chapple et al (1987) suggested that in the two regions they studied (North West and South East Thames) there would be clear savings at hospital level if a DNA screening laboratory were set up in each region. They concluded that their very conservative cost estimates still undoubtedly pointed to a cost-effective service; even more so, they suggested, if one central centre was adopted for London rather than four smaller units for the different regions. The actual costing figures were about £83,000 per annum for staffing and running a screening facility and about £90,000 per annum in cost savings.

Garber and Fenerty (1991) looked into the issue of the costs and benefits associated with a prenatal screening programme for cystic fibrosis (CF). Two broad strategies existed for the control of CF. Firstly, a targeted strategy which reserves prenatal testing for families of children with CF. Whilst a relatively inexpensive method such targeting cannot prevent the birth of the first affected child in each

family. Population-wide screening could detect most affected fetuses, but is a much more expensive and large-scale operation to initiate. Garber and Fenerty identified direct costs of cystic fibrosis as being expenditure for testing, abortion or birth, health care, and all outlay associated with preventing or treating the illness. Indirect costs were seen to include the earnings lost to disease-related disability and early death and nonmedical costs and benefits.

On the basis of targeted testing the net benefits, assuming replacement (ie. replacing an aborted pregnancy with another birth), ranged from about $43,000 to around $70,000 if CF care costs $8,000 annually, to more than $110,000 if CF care costs $20,000 annually. The benefit of testing is about $45,000 greater under replacement than under no replacement at any level of CF costs. Since CF appears in only 1 in 2,000 births in the general population a test applied to all fetuses would need to be extremely specific to avoid the abortion of unaffected fetuses. The authors say, 'the specificity of existing gene probe tests is not known'.

Beech et al (1989) studied the cost of genetic services in the context of DNA probes. They claimed that 'the conclusion emerging is that relative to other new medical technologies DNA probe services are an inexpensive investment'. However, they also assert that 'the conclusion of the paper does mean that the need to express benefits in terms of financial savings is less important. The debate regarding the future of DNA probe services should shift from a financial analysis of whether they can be afforded to a discussion of their future organisation and their merits on ethical and clinical grounds'.

A wider appraisal of the type Beech et al would encourage was attempted by Modell and Kuliev (1991). Their paper proposed a 'general framework for economic analysis that includes non-financial costs and benefits, and the concept of genetic fitness[7]'. They claim that previously most analyses have been carried out to win financial support by demonstrating net benefits. Money has been the main unit of measurement with non-financial costs and benefits excluded as 'intangibles' not susceptible to objective measurement. Modell and Kuliev see the main benefit as being informed choice on the part of couples at risk. Regardless of their final decision, as long as they have been informed and are offered counselling, the object of the service according to Modell and Kuliev has been achieved. They urge a new

7 Modell and Kuliev (1991) claim that the term 'genetic fitness' could be an appropriate criterion for evaluating genetics services. Genetic fitness is determined by: 1. Average final family size compared to the norm for their population group. 2. The proportion of affected children in the families. 3. The proportion of unaffected children in the families. 4. The percentage of wanted pregnancies aborted.

approach where cost and benefits are 'expressed in language compatible with the caring objectives of medicine'. Many health economists may see this as a rather Utopian notion with a better approach being to estimate the quantifiable aspects but stress that this is merely one aspect among many others which must be considered.

The King's Fund forum consensus statement (1987) concludes that 'there is evidence that some programmes pay for themselves from the resources saved by having fewer disabled people. If the condition is fairly common and causes serious disability these savings can be substantial. Even if this were not so such programmes might be justified by their social and clinical outcomes'. Evans and Chapple (1988) suggest that the cost per case prevented is very small when compared to the enormous costs on a year by year basis of caring for children and young adults with these diseases. Thus, economic support for genetic screening and counselling does vindicate their continued existence and expansion but should not be seen as the pre-eminent or only criteria by which to judge their usefulness or benefit to society as a whole. Economic benefits from such programmes are likely to be in addition to wider costs and (likely net) benefits which must also be considered. Thus, economic viability is merely one component among a range of factors that should be assessed with regard to genetic services.

CONCLUSION

The area of genetics and inherited disease is of great importance to many families. Not only are 2-3 per cent of infants born with some degree of genetic disease, but many pregnant women will also want reassurance that their child will be healthy. The role of screening or selective prenatal testing is going to play a more important part in medicine in the future. In the light of both test results and hereditary evidence, non-directive, accurate, informative genetic counselling will be important in order to help prospective parents to make well-informed decisions regarding child-bearing.

The rapid developments currently being seen in molecular genetics augur well for the future prospects of gene therapy and a more complete understanding of the human 'genetic blueprint'. Gene therapy may provide curative possibilities for previously fatal or untreatable ailments. Far from increasing aborted pregnancies this may allow quite severe diseases to be treated at an early stage possibly even inside the womb facilitating the healthy birth of what would otherwise be an abnormal child. If gene therapy does become a routine procedure we may see genetic disease undergoing similar amelioration or elimination to that already seen with infectious and nutritional diseases in the Western world, though we should not blind ourselves to the enormity of the task.

Genetics facilities will have to expand greatly if screening and counselling is to be more widely available as the first stages of this development. The pressures arising to include more genetics education in undergraduate medical courses should ensure sufficient quality and quantity of well trained staff for such centres.

The increasing geographic mobility of people may ensure improved genetic welfare among the world's populations, in addition to advances in the underlying science. This is due to the fact that the less related the couple (small close-knit rural communities, for example, are likely to have many intrafamilial connections) the less likely that they will have the same defective genes thereby reducing the incidence of recessively inherited diseases.

Genetic screening and counselling are inevitably traumatic events for most expectant mothers, even more so if an abnormality is discovered. Counsellors must always be aware of the emotional distress that may easily emerge from a counselling session. The decision to abort or to continue with a pregnancy of an abnormal child will be a difficult one with long-term ramifications whichever choice is made.

The insurance industry has a particular interest in monitoring progress made in genetics knowledge. Life insurance is based on well

established average population risks of dying at certain ages with some lifestyle considerations (eg. smokers premiums may be higher). If an individual person's likely cause of death can be predicted along with roughly when death will take place the whole notion of 'pooling' of risks may no longer exist. Individualised premiums may become established if genetic testing becomes either widespread or even a condition of taking out life insurance. What is clear is that the insurance industry needs to decide its policy now and not when it is forced upon it by technological progress in genetics.

A consensus appears to be emerging with regard to patenting and research in genetics. The original position adopted by some camps in the USA of patenting gene fragments seems to be increasingly unacceptable with the UK stance of only patenting complete gene sequences becoming more generally endorsed. The duration of patent protection is also an important practical and commercial issue in addition to any clinical considerations.

Legal action against doctors is becoming more common in the UK as parents giving birth unexpectedly to abnormal children feel that the abnormality should have been detected earlier in the pregnancy. Affected children may attempt to sue their parents (as has occurred in the USA) if the parents knowingly gave birth to an affected child with a prenatally diagnosed disease. However, the UK does not have the tradition of legal proceedings against the medical profession that can be seen in North America and law suits against the medical profession may remain a relatively unusual occurrence.

The economic evidence, whilst relating almost solely to screening programmes, appears firmly to support the benefits of various screening initiatives which, in most cases, significantly outweigh their costs. Economic savings from genetic services are important but clearly not the sole, or even critical, yardstick by which they should be judged.

Undoubtedly genetics will continue to be an area of active research with new discoveries being made at an unprecedented rate. Once the human gene map becomes more complete and certain diseases become clearly associated with specific gene defects, genetics could develop into the most prominent area of medicine. The ramifications of genetics spread into many fields beyond medical science including ethics, religion and personal insurance.

The emergence of gene therapy may provide a life-line and indeed, if it becomes practical, a cure to many sufferers of genetic disorders. Hopefully chronologists of genetic development, writing in the twenty-first century, will be able to pin-point the 1990s as the decade when quantum leaps were being made both in genetic knowledge and its application to medical treatment.

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