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**GENETIC DISORDERS :  
PREVENTION, TREATMENT,  
AND REHABILITATION**

**Report of a WHO Scientific Group**

WORLD HEALTH ORGANIZATION

GENEVA

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PREVENTION, TREATMENT, AND REHABILITATION

Geneva, 16-22 November 1971

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# **GENETIC DISORDERS : PREVENTION, TREATMENT, AND REHABILITATION**

**Report of a WHO Scientific Group**

A WHO Scientific Group on Prevention, Treatment, and Rehabilitation in Genetic Disorders met in Geneva from 16 to 22 November 1971. The meeting was opened by Dr A. Zahra, Director, Division of Family Health, who welcomed the participants on behalf of the Director-General.

## **1. INTRODUCTION**

In the last decade several aspects of human genetics that are relevant to medicine and public health have been considered by WHO expert committees and scientific groups. This interest in disease of genetic origin results from several considerations : the absolute and relative decline in morbidity and mortality attributable to infection, parasitic infestation, and malnutrition ; the relative increase in morbidity and mortality attributable to genetic factors resulting from the slow changes in gene frequencies ; and the development of promising approaches to the diagnosis, treatment, and prevention of genetic diseases. In a world that views population growth as an important problem and is increasingly concerned with the quality of human life, it will be taken for granted that children should be free of genetic disease.

There is no reliable information on the current prevalence of genetic disease or on the effects that treatment and prevention will have on the number of cases ; these are problems that now need to be studied. Frequencies of individual traits will vary with geographic region, ethnic group, isolate, and deme. The surveys must be both general and particular, and their findings will have both broad and specific objectives. Accurate knowledge about the epidemiology of genetic disease is an important prerequisite of action by a particular community concerning prevention, treatment, and rehabilitation.

In planning health services, it must be remembered that the patient load makes a continuous and in some situations a cumulative demand upon resources.

The resources available to control the expression of genetic disease are not unlimited; some consideration of cost-effectiveness and social value may influence decisions about when and how to apply knowledge to the problem. The responsible health service will have to decide what it can afford to spend on the diagnosis and treatment of genetic disease, and on genetic counselling, taking its other health needs into consideration. At the same time it is important to consider the long-term consequences of any action taken to alter the expression of mutant genes in man.

## 2. THE EPIDEMIOLOGY OF GENETIC DISEASE

Genetic disorders can be either chromosomal or genic. The chromosomal disorders involve the lack, excess, or abnormal arrangement of chromosomes. The genic disorders can be subdivided into those caused by major mutant genes and those that are multifactorially determined, i.e., they result from the interaction of many genes, each with a small effect, are often modified by environmental factors as well, and sometimes involve a developmental or physiological threshold. Genetic disorders make a major contribution to human mortality and morbidity. For instance, some 30% of admissions to one North American paediatric hospital and 40% of paediatric deaths in the United Kingdom are more or less directly related to genetic disease. Each category of genetic disease presents different problems with respect to causes, prevention, diagnosis, and treatment.

### 2.1 Mutation

The origin of genetic disorders is mutation. Broadly defined, mutation refers to any stable change in the genetic material; it includes both numerical and structural chromosomal aberrations, such as extra or missing chromosomes, inversions, translocations, duplications, and deletions, as well as the whole range of single-gene alterations such as duplications, frame-shift insertions or deletions, inversions, and base-pair substitutions.

#### 2.1.1 *Gene mutation*

It was once believed likely that all mutations had a detectable phenotypic effect, usually deleterious. The discovery of an extensive array of genetic polymorphisms in man that have no obvious selective basis has made it clear, however, that many mutations must be virtually neutral in their selective effects. The probability that a random mutation will have a beneficial effect is very small; consequently, most mutations with any detectable selective effect are, in fact, deleterious. In this way mutations give rise in aggregate to the burden of abnormal genotypes documented in Annexes

1, 2, and 3. The strategy of the human geneticist must be to attempt to lessen the harmful effects of mutation, while at the same time preserving the genetic variation in the population that is essential for adaptation and evolutionary progress.

#### 2.1.2 *Chromosomal mutations*

Chromosomal mutations are seldom advantageous although, as in the case of reciprocal translocations, they may have no immediate effect on the carrier. Many chromosomal markers and polymorphic variants detected by the new staining techniques also appear to be without significant phenotypic effects. High-energy radiation, viruses, and chemical agents are recognized causes of chromosome damage; genetically determined host factors are also known to be important, as indicated by the existence of recessive diseases such as Fanconi's anaemia, Bloom's syndrome, and ataxia telangiectasia, in which there is a predisposition to chromosomal breakage and rearrangements. Maternal age is an important predisposing cause of heteroploidy resulting from nondisjunction.

#### 2.1.3 *Causes of mutation*

High-energy radiation is without question the best studied cause of mutation. In recent years, however, increasing attention has been paid to the potential mutagenic (as well as oncogenic and teratogenic) effects of chemical compounds introduced into the environment. In lower organisms many substances are known to cause or enhance mutations, while others have antimutagenic effects. The development of effective techniques for measuring single-gene mutation rates in human fibroblasts will permit the monitoring of potential mutagens on the human genome. During the course of evolution, elaborate and highly specific genetic repair mechanisms have arisen to preserve the fidelity of DNA replication and to protect the organism from mutational damage. A defect in one of these repair enzymes has recently been shown to underlie the predisposition to skin cancer of patients with xeroderma pigmentosum. In this rare autosomal recessive trait there is an extreme sensitivity to the mutagenic effects of ultraviolet radiation. These important findings emphasize the significance of genetically determined host factors in mutation and raise the possibility of modifying this process by pharmacological means.

### 2.2 **Mendelian diseases**

With few exceptions Mendelian diseases are individually rare, since there is strong selection against them and gene mutations are rare events. Nevertheless, as a group these diseases are an important cause of morbidity and death. In one North American paediatric hospital, for instance, they

are responsible for about 7% of admissions, and in the United Kingdom they account for 11% of paediatric deaths (see Annex 1).

### 2.2.1 *Mode of inheritance*

#### *Dominant*

In medical genetics, the term “dominant” refers to genes that produce clinical disease in the heterozygote, as opposed to “recessive” genes that produce disease only in the homozygote. It should be recognized that these are operational terms, and that an increasing number of “recessive” genes may indeed be detected in the heterozygote by appropriate methods.

Dominant mutations are the most easily identified, since the disease occurs in each carrier of the mutant gene. If the mutation is genetically lethal (i.e., prevents reproduction by the affected individual), all cases are sporadic and can be identified as genetic only by indirect means, such as increased paternal age or twin concordance. Individuals carrying dominant lethal mutations will have a birth frequency equal to twice the mutation rate; the less harmful the mutation, the greater the frequency and the lower the proportion of sporadic cases. Rare dominant genes are the most susceptible to selection, natural or artificial, and the conditions they cause will show the most rapid rise in birth frequency following any relaxation of selection due to improved treatment.

#### *Recessive*

Recessive mutant genes produce disease only in the homozygote. Thus, affected children have healthy parents and the family histories are usually negative, although there may be an increased frequency of parental consanguinity. Only a minority of mutant genes, those present in homozygotes, are exposed to selection. Where heterozygotes are detectable by special biochemical tests, identification of high-risk matings before the birth of an affected child is possible.

#### *X-linked*

Most mutant genes on the X chromosome cause disease in hemizygous males but not in heterozygous females. Thus one mutant gene in three is exposed to selection. A few cause disease even in heterozygous females, as in the case of the gene for hypophosphataemia.

### 2.2.2 *Disease frequency*

#### *Principles*

With dominant conditions the reproductive fitness of heterozygotes is the decisive factor governing frequency; there is a simple relationship between the birth frequency of the condition, the mutation rate, and the reproductive fitness of heterozygotes.

With recessive conditions in a population at equilibrium, with no selection for or against the heterozygotes and a constant amount of inbreeding, there is also a simple relationship between birth frequency of the condition, the mutation rate, and the reproductive fitness of homozygotes. If the fitness of heterozygotes is above average, the birth frequency of homozygotes in that population will depend essentially on the balance between the increased fitness of the relatively numerous heterozygotes and the reduced fitness of the homozygotes. A small selective advantage of the heterozygote will result in a relatively high birth frequency of homozygotes even where the disease is lethal.

With X-linked recessive conditions, deviations from the mean in the reproductive fitness of heterozygous females will substantially alter the birth frequency of affected males.

#### *Geographical and ethnic variation*

Some Mendelian disorders show marked variation of birth frequency in different populations. In the case of small isolates the "founder effect" may often explain a relatively high frequency of a sublethal dominant disorder, or of a recessive disorder, even a recessive disorder that is lethal in childhood. In some instances it has been possible to trace the founder, as in the dominant South African form of porphyria, recessive tyrosinaemia (common in a French Canadian isolate), and Ellis-van Creveld syndrome (common in the Amish, a religious isolate in the USA). However, there are also several instances of high birth frequency for serious recessive disorders that involve large populations and are therefore not attributable to the founder effect; examples are cystic fibrosis in Europeans, sickle-cell anaemia in West Africans,  $\beta$ -thalassaemia in Italy and the eastern Mediterranean countries, and familial Mediterranean fever in North Africa and the eastern Mediterranean. In the case of sickle-cell anaemia, the heterozygote advantage is known to consist of resistance to infection with *Plasmodium falciparum*. For the other conditions heterozygote advantage must be presumed, but its nature is not known.

There are other conditions with high birth frequencies in populations of intermediate size, where the relative parts played by the founder effect (or genetic drift) and heterozygote advantage have not yet been evaluated. Examples include the high birth frequency of infantile Tay-Sachs disease in Ashkenazi Jews originating from Poland and Lithuania, and congenital nephrosis in populations of Finnish extraction.

#### *2.2.3 Interaction between genetic and environmental factors*

As shown in Table 1, many diseases are now recognized to result from a deleterious interaction between environmental factors (including drugs) and a specific genotype. Although important in their own right, these

TABLE 1. EXAMPLES OF INHERITED DISEASES WITH ALTERED RESPONSE TO PHARMACOLOGICAL OR ENVIRONMENTAL FACTORS

Trait or deficient enzyme	System affected	Drug or environmental factor	Frequency of trait	Clinical effect
Alcohol dehydrogenase, atypical	Liver	Alcohol	?	Increased tolerance
$\alpha_1$ -antitrypsin deficiency	Plasma	Smoking	Moderately rare	Emphysema
Dicoumarol resistance	Blood-clotting	Dicoumarol	Rare	Decreased response
Ectodermal dysplasia (anhidrotic)	Skin	Heat	Rare	Heat stroke
Glucose-6-phosphate dehydrogenase	Red blood cells	Fava beans, primaquine, etc.	Variable	Haemolysis
Glucuronide transferase	Liver	Salicylates, cortisone	Rare	Jaundice, drug toxicity
Haemoglobin S	Red blood cells	Hypoxia	Variable	Intravascular sickling
Haemoglobins, unstable	Red blood cells	Sulfonamides, oxidants	Very rare	Haemolysis
Isoniazid transacetylase	Liver	Isoniazid	Common	Polyneuritis
Methaemoglobin reductase	Red blood cells	Nitrites, oxidants	Variable	Methaemoglobinemia
Microsomal oxidases	Liver	Dicoumarol	Very rare	Bleeding
Porphyria (some types)	Liver	Barbiturates	Variable	Acute "attacks"
Pseudocholinesterase	Plasma	Succinylcholine	Moderately rare	Apnoea
Subaortic stenosis	Heart	Digitalis	Rare	Output failure
Xeroderma pigmentosum	Skin	UV light	Rare	Cancer

diseases are of particular significance because they may serve as instructive models for other diseases, such as cancer, chronic lung disease, hypertension, atherosclerosis, or the major psychoses, where the exact role and significance of genetic factors is still obscure.

#### (1) *Pharmacogenetics*

Pseudocholinesterase deficiency, glucose-6-phosphate dehydrogenase (G6PD) deficiency, porphyria, and hepatic acetylase deficiency are familiar examples of single-gene mutations that may be responsible for a clinically significant and often life-threatening individual variation in the response to specific drugs.

All of the major modes of inheritance are represented by these disorders. G6PD deficiency is a sex-linked recessive trait in which a variety of drugs may precipitate a self-limited haemolytic anaemia. The trait is common in African, Mediterranean, and Asiatic populations where malaria is or has been endemic. Pseudocholinesterase deficiency and hepatic acetylase deficiency are examples of recessive traits in which the catabolism of, respec-

tively, the muscle relaxant succinylcholine and isoniazid are altered. The former trait is quite rare, but the latter is polymorphic and shows considerable variation in frequency among populations. Finally, acute intermittent porphyria is an autosomal dominant trait in which acute attacks of pain, fever, neuropsychiatric symptoms, and porphyrubinogenuria may be induced by small doses of barbiturates. Misinterpretation of adverse drug reactions may occasionally result in serious harm to the patient. Until proved otherwise, these reactions should be considered to be genetically determined idiosyncrasies, whose careful study could lead to the discovery of important new genetic causes of variation in drug response. This is one group of diseases in which treatment is very straightforward: once the diagnosis has been made the noxious drug should be avoided.

Twin studies constitute a most effective technique for the analysis of variation in drug response.

Maternal drug administration during pregnancy is a recognized cause of fetal malformation and neoplasia. It may have an extraordinarily long latent period, at least in the case of the association between maternal diethylstilbestrol administration and vaginal cancer in the offspring.<sup>1</sup> The extent to which genetic sensitivity of the mother or the fetus may be involved in these reactions is unknown.

### (2) *Environmental agents*

A number of genetic traits are associated with unusual sensitivity to common factors in the environment. Homozygotes and possibly heterozygotes for  $\alpha_1$ -antitrypsin deficiency appear to be predisposed to the development of emphysema, and interaction with environmental agents, such as cigarette smoke, may have deleterious effects. There is an unusual sensitivity to ultraviolet light in xeroderma pigmentosum, and to high temperatures in anhidrotic ectodermal dysplasia. Certain individuals with G6PD deficiency may develop acute haemolysis upon exposure to fava beans. In all these disorders, environmental modification may provide an approach to prevention.

### (3) *Maternal effects*

Maternal effects represent a special type of environmental interaction that is relevant to the treatment of genetically determined metabolic disorders. It is now well established that women who have hyperphenylalaninaemia during pregnancy are at high risk of bearing defective offspring with every pregnancy, not because the fetus is homozygous for phenylketonuria but because it develops in an environment with an excess of phenylalanine. Preliminary success has been reported in preventing fetal damage in this

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<sup>1</sup> Herbst, A. L., Ulfelder, H. & Poskanzer, D. (1971) Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumour appearance in young women. *New Engl. J. Med.*, **284**, 878.

situation by dietary control of maternal phenylalanine levels during pregnancy. However, the efficacy of maternal dietary control in preventing minor degrees of retardation remains to be established. To the extent that maternal effects occur in females treated for genetic disorders, the benefits they derive from this treatment may be offset by the birth to them of defective offspring.

There is an urgent need for information concerning possible maternal effects of other genetic diseases so that the total impact of treatment can be evaluated. Diabetic fetopathy and Rh immunization are examples of diseases resulting from adverse reactions between the mother and fetus. For many years it has been known that the development of erythroblastosis caused by Rh incompatibility was to some extent prevented by simultaneous ABO incompatibility, because naturally occurring ABO antibodies removed fetal cells from the maternal circulation before they could stimulate the production of Rh antibodies. This protective mechanism has been exploited therapeutically with the development of specific antibody injections that prevent maternal Rh sensitization.<sup>1</sup>

### 2.3 Multifactorial disorders

#### 2.3.1 *Phenotypic manifestations*

These manifestations are of two types :

(1) *Continuous*. Some disorders represent merely an extreme value of a continuously distributed variable, most values of which are normal or nearly normal. The distinction between normal and abnormal values is made in terms of an arbitrary threshold, as with essential hypertension, essential hypercholesterolaemia, or mental retardation. The continuous distribution is usually caused by both genetic and environmental variation. The genetic component is usually polygenic, depending on minor contributions of many gene loci rather than on a major effect of a single gene. The relationship between the primary products of the genes involved and the development of the phenotype is indirect. There is therefore an opportunity for environmental factors to modify the expression of these genes, so that the disease is of multifactorial etiology with both genetic and environmental components.

(2) *Discontinuous*. Many common disorders at first sight appear to represent a discontinuous variation. Individuals are either affected or unaffected. For some such disorders, however, there is good reason to suppose that there is an underlying continuously variable liability to the disorder, with a threshold beyond which individuals are clinically affected.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 468.

The family patterns found with most of the common congenital malformations indicate that these disorders depend on a specific continuous liability that is multifactorially determined, and that a substantial proportion of this liability is due to genetic variation. There are also indications that most of the common disorders of adult life in developed countries, such as duodenal ulcer, schizophrenia, and ischaemic heart disease of early onset, are semi-quantitative conditions with a multifactorial etiology.

### 2.3.2 Frequency

#### *Ethnic and geographic variation*

The frequency of multifactorial disorders is high compared with that of Mendelian and chromosomal disorders. Some have an apparently similar frequency in many different populations. The proportion of individuals who develop schizophrenia at some time of their lives appears to be similar (8–10 per thousand) in many different populations. Reports from several countries indicate that congenital heart malformations total 4–6 per thousand total births. On the other hand, the frequency of early-onset ischaemic heart disease shows marked variation. Similarly, the frequency of the neural tube malformations varies markedly, e.g., 7–8 per thousand total births in Ulster and Wales, 4 per thousand in south-east England, 2–3 per thousand over most of Europe, and less than 2 per thousand in African and eastern Asian populations. These variations tend to persist after migration.

#### *Secular variation*

Although the frequency of some multifactorial conditions may change rapidly, the frequency of others appears to be fairly constant. The frequency of death from ischaemic heart disease has increased markedly over the past 60 years in Europe. Furthermore, certain African populations have rapidly acquired European frequencies of ischaemic heart disease when they have adopted a European diet and way of life. No consistent secular changes have been observed in the frequency of most of the commoner congenital malformations.

#### *Seasonal variation*

Small but consistent seasonal variation is seen in the birth frequencies of certain congenital malformations. In some populations the neural tube malformations have a peak frequency among spring births and congenital dislocation of the hip reaches a peak among winter births.

#### *Variation by maternal age and birth order*

Excessive frequency of neural tube malformations is associated with first births and with high birth orders and late maternal age.

*Variation by socioeconomic status*

Several multifactorial conditions with onset in adult life show variations in frequency linked with socioeconomic status. The neural tube malformations, in particular anencephaly, show a marked variation in birth frequency between groups of different socioeconomic status in the British Isles, especially Scotland, and also in North America. This association occurs within ethnic groups.

*Empirical risks*

Empirical risk figures for familial recurrence are available for many multifactorial conditions. Those for congenital malformations were recently considered by a WHO Scientific Group.<sup>1</sup> In the case of schizophrenia the proportion of first-degree relatives of probands who are affected by the disease is about 1 in 10, and recent studies indicate that this risk also applies when the child of a proband is adopted into another family at birth. In the case of ischaemic heart disease, the frequency among first-degree relatives is about 5 times that in the general population.

In contrast to Mendelian traits, the recurrence risk of multifactorial conditions is much influenced by the number of affected persons already present in the family.

*Heterogeneity*

The multifactorial disorders are heterogeneous in the sense that the relative contributions of genetic predisposition and environmental factors to the etiology will vary greatly from patient to patient. However, it is important to remember that among phenotypes that are largely multifactorial, there will often be a small proportion determined by major mutant genes. Perhaps about 10% of subjects with ischaemic heart disease of early onset (before the age of 55 years) are heterozygotes for the gene causing "familial" hyper- $\beta$ -lipoproteinaemia. A majority of the rare subjects who die from ischaemic heart disease before the age of 25 are homozygous for this gene. In a small proportion of patients with cleft lip (with or without cleft palate), the condition is not multifactorial but determined by a single gene, as in the lip-pit syndrome.

### 2.3.3 Predisposing causes

*Genetic variation*

Where inheritance is polygenic, research should be aimed at identifying the single gene loci involved and the mechanisms by which they act. It has been shown that an approximately normal distribution of polygenic disorders can result from the segregation of relatively few genetic differences.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1970, No. 438.

Furthermore, some of the genes involved in a multifactorial system may have major effects on the system, e.g., a gene for joint laxity that predisposes to dislocation of the hip, or a gene causing ocular hypertelorism predisposing to cleft palate. In other cases a gene with minor effects on the system may have major effects elsewhere that permit it to be identified, as with the effect of the ABO and secretor loci on duodenal ulcer. Finally, even where the individual genes cannot be distinguished, it may be possible to identify their point of action — for example, the multifactorial system that causes the shallow acetabulum predisposing to dislocation of the hip, or the genes that modify face shape in a way that increases susceptibility to cleft lip.

Recognition of how the individual genes of the multifactorial system act to modify susceptibility promotes understanding of how the defects arise, and should lead to improved ability to predict risks of recurrence.

#### *Environmental factors*

On the other hand, the fact that frequencies of multifactorially determined disorders vary with such environmental features as socioeconomic status, season of birth, and parental age means that there may be specific environmental factors predisposing to the disorder in question. The problem is to define them. Progress is being made in some cases, as for instance in identifying the influence of smoking, diet, obesity, and lack of exercise on ischaemic heart disease, and the influence of methods of swaddling on dislocation of the hip. In other cases, such as the variation of anencephaly with socioeconomic status, the relevant factor remains to be found. Once the subjects who are genetically at risk can be recognized and the environmental factors are known, preventive treatment may become feasible.

## **2.4 Cytogenetic disorders**

The true frequency of cytogenetic disorders of conception can be estimated most closely by karyotypic analysis of early human embryos. However, such investigations can be carried out only in countries where abortions are legal. Estimates may also be based on cytogenetic investigations of spontaneous abortions, stillbirths, and newborn babies. Sex chromosome surveys have the advantage of simplicity, but provide information only on numerical variations of the X chromosomes.

The incidence of chromosomal aberrations in karyotypes of unselected newborn infants in series from several countries is about 0.5%. However, the techniques used were not effective in detecting mosaicism and minor deviations; the actual incidence must therefore be higher and probably approaches 1% in view of the proportion of mosaics found in patients.

At present more than 300 numerical and structural types of chromosomal aberration have been described. The most important numerical aberrations are the syndromes of Down, Klinefelter, and Turner, while the major

structural aberrations include the cri-du-chat syndrome and the deletion of chromosome 18.

Data from different countries on the incidence of sex chromosome aberrations agree fairly well, but most samples are rather small. A comparison of large samples from Edinburgh and Moscow, however, shows a significantly lower incidence of the triple-X syndrome in Moscow. The average incidence of sex chromosome aberrations based on all reported samples is 0.24%.

Differences between different countries in the incidence of Down's syndrome have been reported, but the figures are difficult to evaluate because the methods of ascertainment and identification were different. The overall incidence is 0.14%.

Very little is known about the factors that cause chromosomal disorders in man. The most important finding is the association between increasing maternal age and Down's and Klinefelter's syndromes in particular. A decrease in the frequency of childbirth in older mothers could lead to a significant reduction in the incidence of nondisjunctional aneuploidy. Other factors such as genetic predisposition, autoimmune disorders, viruses, chemical mutagens, and radiation are currently being investigated.

A high incidence of chromosomal disorders is associated with certain conditions, the most important being early spontaneous abortions (60%), multiple congenital malformations (5-20%), infertility and sterility in different groups of patients (1-10%), and mental retardation (1-3%).

In most instances the chromosomal disorders occur as new mutations, i. e., both parents are normal and the risk of recurrence is low. However, there is an important minority of cases where one parent is the carrier of a chromosomal rearrangement or mosaicism. In such families the recurrence risk may be 10% or higher.

Recent technical developments, such as fluorescent staining and modifications of Giemsa staining, have made the identification of chromosomal variations more precise. This will be valuable in genetic counselling and will lead to the detection of new associations between chromosomal aberrations and pathological deviations. These developments will doubtless lead to revision of the estimates of the total frequency of chromosomal aberrations in man.

### 3. PREVENTION AND TREATMENT

#### 3.1 Prevention of defective genotypes

Prevention of genotypes associated with disease or malformation requires the identification of matings that are capable of producing such genotypes. These may be matings of individuals carrying, or likely to be carrying, a dominant or X-linked recessive gene or a balanced translocation, or matings

between carriers of a deleterious recessive gene. Such individuals are usually identified through an affected child or other near relative, in which case the counselling may be termed retrospective, as opposed to prospective counselling where the defective genotype has not yet occurred in the family.

### 3.1.1 *Prospective genetic counselling*

Although most counselling at present is retrospective, it would be much more effective to counsel the high-risk family before they have an affected child, i.e., prospectively. This requires identifying heterozygous individuals by some sort of population screening procedure, and carefully explaining to them the risk of their having affected children if they marry another heterozygote for the same gene.

The development of techniques suitable for use in mass screening, and increased awareness of the significance of this approach for public health policies, has led to the initiation of screening programmes for several diseases, and the number is likely to increase as methods improve.

At present this approach is limited to populations in which the frequency and severity of a particular disease are high. There are, for instance, programmes directed against sickle-cell disease in populations of West African origin, against G6PD deficiency and thalassaemia in populations of Mediterranean origin, and against Tay-Sachs disease in Ashkenazi Jews. The technology and logistics have been worked out and appear feasible. Such programmes entail a commitment to provide counselling for identified heterozygotes.

Informing an individual identified by a screening programme that he or she is carrying a specific mutant gene that may cause disease in the children if he or she chooses a certain type of mate is quite a different thing from counselling parents who have already had an affected child. Virtually nothing is known about the psychological effects of discovering that one carries a "bad" gene, or about the kinds of social pressure that may be brought to bear on an individual so identified.

Any such screening programme should be accompanied by a well designed public education campaign, and the early stages of such programmes should include intensive study of their psychological and social implications.

In some cases it may be possible to reduce the frequency of matings between heterozygotes without identifying them specifically. For instance, if all Ashkenazi Jews married outside their community the frequency of Tay-Sachs disease would be much reduced. However, this approach depends on the gene in question having a high frequency in one community.

### 3.1.2 *Retrospective genetic counselling*

The choice of the method for preventing the recurrence of a genetic disorder depends on its recurrence rate and severity as well as on the attitudes

and cultural environment of the couples involved. The method must be acceptable to the couple and their society and in accordance with the customs and laws of their country. With these considerations and restrictions in mind, one of the following preventive methods could be suggested.

(1) *Contraception.* Although no method of contraception is entirely reliable, modern methods are highly effective and are acceptable in many cultures.

(2) *Pregnancy termination.* This may have to be considered in cases where advice is sought after the woman has become pregnant. Termination, if found necessary, is acceptable and legal in several countries during the first months of pregnancy. The legal limit varies from country to country. Termination late in pregnancy carries greater risk. Whenever possible, amniocentesis should be used to diagnose the genetic defect in the fetus.

(3) *Sterilization.* This procedure, performed at the request of either the husband or the wife, is the most radical method of contraception and is at present irreversible in most cases. It is usually requested only where there is a high recurrence rate for a severe genetic disorder.

It should definitely be discouraged in young couples, who may in the future decide to change their marital partner or resort, for example, to artificial insemination with donor semen (AID), thus enabling the wife to bear and raise a normal child. Future progress in prenatal diagnosis or treatment might also enable some affected women to have normal children.

### 3.2 Screening for genetic disease

Screening has an obvious objective: to improve the quality of life for individuals and society as a whole by permitting the control of disease in affected persons.

How screening for certain types of genetic disease might benefit the health of man has already been considered by a WHO Scientific Group.<sup>1</sup> Since the Group's report was published the technology of screening has expanded considerably, and as a consequence the number of diseases susceptible to prophylactic and preventive measures has greatly increased.

Screening for genetic disease is synonymous with early and mass detection; the objective is to detect the trait early enough to prevent harmful expression of the mutant allele. Ascertainment may be attempted prenatally or postnatally; prenatal detection is dealt with in section 3.3. For postnatal detection of genetic traits screening is generally performed in the immediate postnatal period so that prophylactic treatment may begin before the clinical phenotype is fully expressed; screening for phenylketon-

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 401.

uria is an example. Screening for traits that are harmful only in association with certain environmental factors is also important to those who inherit the trait, since they may then be counselled to avoid the provocative agent.

A screening programme may also have a public health objective. In this case, the cost of detection and subsequent counselling and treatment should be offset by the saving brought about by preventing disease and thereby obviating the need for patient care. For example, the incidence of Down's syndrome could be reduced by about one half by a programme of prenatal screening in the 10% of pregnancies that occur in women over 35 years of age, with selective termination where indicated. The cost of such a programme would be substantially less than half that of institutional care for the trisomic population.

The cost of diagnosis and treatment of phenylketonuria in North America is now about one-third of the cost of institutional care for the retarded phenylketonuric who has not received the benefit of early diagnosis and treatment. Moreover, the emotional and psychological benefits to the individual and society brought about by disease prevention are incalculable.

The problems of diagnosis in screening programmes have been much discussed. The occurrence of phenocopies and genetic heterogeneity confuses the interpretation of the "positive test" in the programme searching for an index trait. This problem is encountered whether the screening is done at the level of the clinical phenotype, the biochemical phenotype, or the gene product. Now that screening for the heterozygous state is technically feasible for many traits it should be recognized that, because of genetic heterogeneity, it may be hazardous to predict the homozygous phenotypes from observation of the heterozygotes. Incomplete ascertainment and misinterpretation will undoubtedly continue to hamper attempts to modify the expression of genetic disease.

### **3.3 Prenatal diagnosis**

#### **3.3.1 *Amniocentesis***

The use of transabdominal amniocentesis to obtain amniotic fluid and cells from the fetus at 14-16 weeks of pregnancy has added a new dimension to genetic counselling. It permits diagnosis of genetic disease at an early enough stage to terminate the pregnancy so as to prevent the birth of a defective child. This allows high-risk couples the opportunity to have only unaffected children.

In expert hands, the technique is reasonably safe for the mother and very few ill-effects on the baby have been reported. However, the possibility of long-term detrimental effects has not been ruled out, since the procedure has only recently been introduced; new and existing programmes should include careful long-term assessment. Furthermore, the technique is not

simple, and should be performed only in centres where specially trained personnel are available:

*Cytogenetic diagnosis*

By culture of fetal cells from the amniotic fluid, the karyotype of the fetus can be established and chromosomal aberrations can be detected. With standard methods of karyotyping, interpretation of the results can sometimes be ambiguous. However, the development of improved staining methods will allow much better definition of cytogenetic abnormalities and greatly improve their usefulness in prenatal diagnosis.

Considerations underlying the development of criteria for cytogenetic screening have been discussed in sections 2.4 and 3.2. Amniocentesis is generally considered suitable:

- (1) where one of the parents carries a translocation or other chromosomal aberration, or an abnormal stem-line;
- (2) in older mothers, the lower limit depending on the availability of facilities.

Widespread application of amniocentesis in older women would lead to a significant reduction in the frequency of children born with chromosomal aberrations.

*Biochemical, immunological, and histochemical diagnosis*

A small but growing number of diseases can be diagnosed *in utero* (see Annex 2), either by histochemical techniques applied to the cells directly, by histochemical or biochemical tests on cultured cells, or by measurement of constituents of the amniotic fluid. It should be emphasized that many of these techniques are reliable only in expert hands, and that there is still not enough precise information about how the biochemical characteristics of cells vary with gestational age, conditions of culture, etc.

The applications of amniocentesis would be greatly expanded if it were possible to obtain tissue, particularly blood, from the embryo without damaging it. For instance, a micro method is now available for detecting the presence of haemoglobin S in the fetus at about 14 weeks of gestation, but the use of the technique awaits a method of obtaining fetal blood. This would also make possible the use of genetic markers, such as blood groups, in cases where there is close linkage with the abnormal gene.

The availability of prenatal diagnosis for certain diseases makes it possible for parents of a child with one of these diseases to have further children without fear, provided they are willing to have the pregnancy terminated in the event of a recurrence. Coupled with population screening (in cases where the gene frequency is high enough to warrant this), prenatal diagnosis could result in a marked decrease in the frequency of genetic diseases (see section 5).

### 3.3.2 *Examination of the fetus*

Noteworthy advances are being made in methods of examining the fetus, either directly or indirectly, and may lead to the first substantial reduction in frequency of the more serious external malformations.

*Contrast radiography* may permit the diagnosis of relatively gross malformations such as anencephaly.

*Ultrasonic scanning* is becoming an increasingly precise method of fetal visualization, but is at present limited to fairly gross malformations.

Perhaps the most promising approach is *direct visualization* of the fetus by the use of fibre optics. Instruments are now available that permit good visualization and even photography of fetuses. The technique has been used in pregnancies where there is a high risk of anencephaly and/or spina bifida (parents of two affected children). Further improvements in technique are needed.

Finally there is the possibility of detecting gross sensory or neuromuscular defects by applying to the fetus appropriate physiological tests, ranging from simple observation of fetal movements or reflexes to electrocardiography. Such techniques are being developed and may well make useful contributions to prenatal diagnosis.

## 3.4 **Therapy**

### 3.4.1 *Prophylaxis*

Prophylaxis of the manifestations of genetic metabolic diseases can be achieved by a variety of approaches. Some disorders of the amino acid, carbohydrate, and certain other metabolic pathways susceptible to prophylaxis are listed in Table 2. These disorders are amenable to substrate reduction, to cofactor supplementation, to metabolite or enzyme replacement, to removal of toxic products, or to other techniques for neutralizing the mutant genotype. For most of the disorders in Table 2, prophylaxis is possible only if the disease is diagnosed very early, since damage to various organs may start in infancy, in the neonatal period, or even prenatally. Some disorders are so rare, or have so recently been discovered, that there is not yet sufficient evidence to decide if complete suppression of clinical manifestations is really possible. There are, in fact, very few diseases for which there is satisfactory proof that treatment can prevent all clinical manifestations. In some other disorders, such as cystinuria, histidinaemia, hyperphenylalaninaemia, and even "classical phenylketonuria", which are undoubtedly genetically heterogeneous traits, clinical manifestations may not develop at all in some untreated patients, so that critical assessment of the value of prophylactic therapy becomes problematic. The possibility

TABLE 2. SOME GENETIC METABOLIC DISEASES  
SUSCEPTIBLE TO TREATMENT

Disease	Treatment	Efficacy of treatment
<i>Amino acid metabolism</i>		
Phenylketonuria	Phenylalanine-restricted diet	Good if started in first two months of life
Maple syrup urine disease	Diet restricted in leucine, isoleucine, and valine	Fair if started in neonatal period
Homocystinuria	Diet restricted in vitamin B <sub>6</sub> and methionine; addition of cystine	Not yet known
Histidinaemia	Histidine-restricted diet	Not yet known
Tyrosinaemia	Diet restricted in phenylalanine and tyrosine	Not yet known
Cystinosis	Diet restricted in methionine and cystine; kidney transplantation (symptomatic)	Not yet known
Cystinuria	Alkali, high fluid intake, D-penicillamine	Good for prevention of urolithiasis
Diseases of the urea cycle (some forms)	Protein-restricted diet	Fair, but limited experience
Glycinaemias (some forms)	Protein-restricted diet	Fair, but limited experience
<i>Carbohydrate metabolism</i>		
Galactosaemia	Galactose-free diet	Good if started in neonatal period
Fructosaemia	Fructose-free diet	Good if started in early infancy
Malabsorption of di- and monosaccharides	Monosaccharide-free or disaccharide-free diet	Good
<i>Other metabolic pathways</i>		
Wilson's disease	D-penicillamine, potassium sulfide, Cu-restricted diet	Fair or better
Primary haemochromatosis	Removal of Fe by phlebotomy, deferoxamine	Fair
Pyridoxine dependency	High doses of pyridoxine	Can be good if started in neonatal period
Familial hyperlipoprotein-aemia	Fat restriction, use of medium-chain fatty acids, cholestyramine, clofibrate	Fair
Familial defective synthesis and delivery of thyroid hormone (familial goitre)	Levothyroxine or desiccated thyroid	Good
Adrenogenital syndrome	Cortisone; mineralocorticoids in patients subject to salt loss	Good
Cystic fibrosis	Pancreatic extracts, diet, bronchial mucolytics, etc.	Short-term prognosis much improved; long-term prognosis unknown

TABLE 2 (continued)

Disease	Treatment	Efficacy of treatment
Crigler-Najjar syndrome	Blood exchange transfusion, glucuronyl transferase stimulation by phenobarbital	Unsatisfactory long-term results
Nephrogenic diabetes insipidus	High fluid intake of low osmolarity, saluretics	Good if started in early infancy
Rickets refractory to vitamin D	Vitamin D and phosphate salts	Fair or better
Renal tubular acidosis (Butler-Albright syndrome)	Alkali therapy	Good

of genetic heterogeneity for any trait must be considered, since this may influence treatment.

The following prophylactic procedures have so far been used :

(1) *Substrate reduction*

This type of therapy is used for most inborn errors of amino acid and carbohydrate metabolism. It is successful where metabolites accumulating proximal to the enzyme block interfere directly or indirectly with the development or function of one or more organs, and in particular with the brain. The exact mechanism of such interference is not yet known. Substrate reduction may be achieved by omitting "non-essential" or essential nutrients from the normal diet. Several aminoacidopathies have been successfully treated by specific limitation of the relevant amino acid, while for others it suffices to offer diets that restrict the total protein intake.

(2) *Cofactor supplementation in pharmacological doses*

This therapeutic principle is well illustrated by the use of high doses of pyridoxine in homocystinuria. Pyridoxine acts as cofactor for the enzyme cystathionine synthetase, and in more than half of patients with homocystinuria, substrate accumulation before the block can be virtually eliminated by large doses of pyridoxine, without other modification of the diet. There are at least a dozen traits in which vitamin responsiveness reflects a particular mechanism whereby cofactor metabolism and substrate metabolism interact.

(3) *Metabolite replacement*

Metabolite replacement can be carried out in a variety of disorders where deficiency of a metabolic or biosynthetic product is an important

determinant of the genotype, such as familial goitre or the adrenogenital syndrome. This treatment also deserves consideration in some aminoacidopathies, where substrate reduction alone may be inadequate, e.g., cystine replacement in homocystinuria, and tyrosine replacement in phenylketonuria.

(4) *Removal of toxic products*

This therapeutic principle overlaps with those dealt with under (1). For example, metabolites such as galactose,  $\alpha$ -ketoisocaproic acid, and phenylalanine are believed to have a "toxic" action in high concentrations. Copper accumulation in Wilson's disease, iron accumulation in primary haemochromatosis, or bilirubin excess in the Crigler-Najjar syndrome are regarded as toxic; these products can be removed by penicillamine, phlebotomy and deferoxamine, and exchange transfusions respectively, although the last procedure is inadequate for long-term prevention of clinical manifestations.

(5) *Dietary supplements*

Supplementation of the diet with various physiological substances may be necessary for prophylactic therapy. For example, water supplementation in nephrogenic diabetes insipidus, and alkali supplementation in renal tubular acidosis (Butler-Albright syndrome), are effective forms of prophylactic treatment if started early enough after birth.

(6) *Enzyme replacement*

Deficiency of enzyme activity can be corrected, in theory, by replacement of the enzyme. This is done, for example, in the treatment of trypsinogen deficiency and of some blood-clotting disorders. The procedure requires a source of enzyme, and a route of administration whereby the enzyme may come into effective contact with the substrate. Unavailability of the enzyme, rapid inactivation or low activity *in vivo*, and immunological intolerance to repeated exposure to "naked" enzymes complicate this approach to therapy. Some of the hazards and benefits of this treatment are illustrated in patients with metachromatic leukodystrophy (where arylsulfatase A infusion has no effect on brain enzyme concentration), type II glycogen storage disease (where  $\alpha$ -glucosidase infusion was followed by severe immunological intolerance), and Hunter's and Hurler's syndromes (where infusion of normal leukocytes is tolerated and followed by a marked increase in the urinary excretion of mucopolysaccharides and by improvement of joint mobility and clinical appearance).

### 3.4.2 *Symptomatic therapy*

So far this section has dealt mainly with the prophylaxis and treatment of inborn errors of metabolism. It has established some general principles that it is hoped will make it possible to treat many more genetic diseases once the specific metabolic error has been found. However, a great many more genetically determined conditions, both Mendelian and multifactorial, can now be effectively treated by surgical and other means, whereby the survival rate and the reproductive fitness of the patients are greatly improved.

Some examples of such treatment of Mendelian conditions are surgery for genetic types of congenital cataracts, for retinoblastoma, for multiple polyposis of the colon, and for genetic types of craniostenosis. With regard to multifactorial congenital malformations, the problem of congenital dislocation of the hip has largely been solved by early screening and early treatment. Effective surgical treatments are available for cleft palate, club foot, pyloric stenosis, and aganglionic megacolon. Of infants with congenital heart disease, about 60% of those surviving the first 3 months of life can be effectively treated by heart surgery. Some 40% of those infants with meningomyelocele who survive the first day may be expected, with treatment, to reach adulthood; in a group of live-born subjects in London, 66% survived until the end of the first year and at least 50% may be expected to survive to adult life.<sup>1</sup> Among multifactorial diseases of adult life, new pharmacological treatments for psychiatric disorders (e.g., schizophrenia) have greatly reduced the time patients need to be hospitalized and are therefore likely to increase reproductive fitness. Some success has also been achieved in treating the symptoms of chromosomal diseases, as with the hormonal treatment of Turner's and Klinefelter's syndromes and of some patients with ambiguous genitalia, although on the whole such treatment has not increased reproductive fitness.

Experience with organ and tissue transplantation is limited. Normal leukocyte infusion in mucopolysaccharidosis holds promise. Bone marrow transplantation in the immune deficiency syndromes has been attempted and is under intensive evaluation. Transplantation of liver in Wilson's disease has been performed with short-term success. Liver transplantation may prove valuable as a source of enzyme in many hereditary metabolic traits. Renal transplantation in Fabry's disease is said to have a dramatic beneficial effect on the phenotype; the same technique in cystinosis corrects the uraemic nephropathy only and does not modify the cystine storage in other tissues; small deposits of cystine may appear in the donor kidney with time, presumably from reticuloendothelial entrapment of cystine from circulating white blood cells.

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<sup>1</sup> Carter, C. O. (1971) In: Norman, A. P., ed., *Congenital malformations in infancy*, 2nd ed., Oxford, Blackwell, chapter 1.

### 3.4.3 *Duration of therapy*

For most of the diseases listed in Table 2 the length of time for which specific treatment needs to be continued is not yet known. This can be determined only by long-term observation and critical assessment of the results. From experiences in phenylketonuria there is reason to believe that disorders interfering with myelin synthesis may need strict therapy only until myelination of the brain is practically completed, i.e., at about puberty. Dietetic treatment of disaccharide and monosaccharide malabsorption may be relaxed after infancy and early childhood as the intestinal tolerance of the patient increases. Restriction of galactose and fructose in the diet of subjects with galactosaemia and fructosaemia can relatively easily be maintained over the whole course of the disease, and this policy is recommended until more is known about the long-term risk of hepatic damage and cataracts.

Prevention of stone formation in cystinuria is not age-limited, nor is the prevention of copper accumulation in Wilson's disease, of iron accumulation in primary haemochromatosis or of lipoprotein accumulation in familial hyperlipoproteinaemia. Hormonal substitution in familial goitre and in the adrenogenital syndrome should also continue into adult life, as should the treatment of nephrogenic diabetes insipidus, rickets refractory to vitamin D, and the renal tubular acidosis of the Butler-Albright syndrome, although the dosage of water, vitamin D, and alkali respectively can be related to the needs of the older patient.

## 4. RESOURCES

The prevention and treatment of genetic diseases and the rehabilitation of patients require a wide range of support facilities.

### 4.1 Resources for counselling

Various aspects of genetic counselling<sup>1</sup> and a methodology for family studies of genetic factors<sup>2</sup> have been discussed by previous groups of experts convened by WHO.

#### 4.1.1 *Periodic counselling*

The need for genetic counselling services is likely to increase markedly in the future, because of more frequent recognition and referral by the health profession, the introduction of population screening programmes, and increased public interest. In order to meet this growing demand, the

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1969, No. 416.

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 466.

establishment of counselling centres and the training of competent counsellors should be given priority.

Access to available counselling facilities may be limited by ignorance of their existence. Directories of the location and scope of counselling centres would help physicians and others to refer patients to a qualified source of information. As medical genetics matures as a scientific discipline, it will be necessary to find ways of ensuring professional competence.

The role of the genetic counsellor should be to assist the physician with diagnosis, to estimate the recurrence risk, to interpret this information to the patient in meaningful terms, and to help the patient to reach and act upon an appropriate decision. The counsellor must have extensive knowledge to fulfil this role adequately. If he is to reach a correct diagnosis, moreover, support facilities at the clinical and laboratory levels may be required.

Taking the family history is vital but time-consuming. Time itself is therefore an important resource for which provision must be made. Time is also needed for the counselling process, which may involve several interviews, searching of records, and arranging for diagnostic tests. Follow-up interviews may also be desirable. Records should be kept, and may be incorporated into genetic registries or record-linkage programmes.<sup>1</sup> Counselling centres are unlikely to have available the wide variety of resources to meet all possible needs. In the case of hereditary metabolic disease, for example, no single centre will be able to perform all the biochemical tests, enzyme assays, histochemical procedures, etc., required for counselling in every situation. A network of centres can meet this need, if the individual centres complement each other in the range of tests offered. Some parts of the world now have such networks, sponsored either by private organizations or by governments.

#### 4.1.2 *Continuous counselling*

Genetic disease susceptible to prophylactic or symptomatic treatment requires continuous, long-term supervision, with careful follow-up to assess the efficacy of the treatment. Often there is also a need for prospective counselling of the patients and their families. These needs are particularly apparent in the small but prototypical group of patients with hereditary metabolic disease. Cost-accounting for the resources required is often possible, and will assist a community to decide whether to establish and maintain various phases of genetic disease control.

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<sup>1</sup> Acheson, E. D., ed. (1966) *Record linkage in medicine*, London, Livingstone.

### *Case ascertainment*

The establishment of support facilities often begins with programmes<sup>1</sup> concerned with prenatal diagnosis, mass postnatal detection, or special screening of high-risk populations. Clearly mass screening must be accompanied by appropriate treatment facilities. Accurate diagnosis, and the availability of regional or central support facilities to confirm presumptive positive tests, are essential. Where tests prove positive, it must be possible to find the patients concerned quickly, whether they live in densely populated regions or are scattered over a large geographical area. Delay in reaching the patient to confirm the diagnosis and initiate prophylaxis may render all previous efforts useless.

Follow-up after diagnosis should include identification of family members at high risk for the trait present in the propositus. Failure to do this will reduce the efficiency of diagnosis and prevention, and mean that the obligations of the programme towards the propositus are only partially fulfilled.

### *Monitoring of therapy*

Prophylaxis requires careful monitoring of therapeutic effects. Apparent failures of treatment may be the fault not of the prescription, but of the way in which it is administered. A system of monitoring is therefore required to ensure that the patient does not deviate from the prescribed treatment regimen, particularly where "environmental engineering" is employed to neutralize the effect of the mutant allele(s).

Treatment programmes will become increasingly polyfunctional as screening widens in scope and as patients with many types of genetic disease are identified. A team approach can meet the demand for professional expertise in the management of a wide variety of genetic diseases.

The patient is best treated in his natural environment, not at exorbitant cost in the medical centre; home care programmes are therefore desirable. A model for a polyfunctional programme has been described;<sup>2</sup> it indicates how continuous counselling by telephone and home visits can cope with the common problems found in association with the hereditary illness, and how treatment effects can be monitored. The cost of such facilities can be low, and in the example cited the savings derived from diminished use of hospitalization and other traditional modes of care amounted to half the cost of the programme itself. Thus regional treatment centres can, to some extent, pay their own way while improving patient care.

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 401.

<sup>2</sup> Clow, C. L., Reade, T. M. & Scriver, C. R. (1971) Management of hereditary metabolic disease: the role of allied health personnel. *New Engl. J. Med.*, **284**, 1292-1298.

## 4.2 Resources to meet anticipated future needs

### 4.2.1 *Prenatal diagnosis*

The demands for prenatal diagnosis are likely to increase relatively soon, particularly when population growth becomes a universal concern, or if the mean maternal age for childbearing rises. The facilities needed to cope with prenatal diagnosis and the associated commitments are complex, and involve trained personnel, special equipment, and many technical procedures. It is unlikely that prenatal diagnosis, as now understood, will ever be undertaken lightly. Centres for prenatal diagnosis will be required to serve regional needs; they should be coordinated so that the diagnostic services they provide are complementary.

### 4.2.2 *Treatment facilities*

Improved symptomatic and prophylactic treatment will increase the patient load in various ways. Two examples are given below:

(1) Successful treatment of a female with a metabolic disease will increase the risk that a fetus she bears will be harmed during its development in the maternal environment, unless she is again (or continuously) exposed to prophylactic treatment, and even then the safety of the fetus is not assured. Registers to identify such females at risk and facilities to provide acceptable treatment may be desirable. Further research on the feasibility, acceptance, and safety of prophylactic treatment during pregnancy is also urgently required. The problem already concerns several hundred women per year in those communities where mass screening and prophylactic treatment are now practised.

(2) Symptomatic treatment of genetic conditions such as pyloric stenosis, cleft lip, and neural tube malformations will substantially alter the reproductive fitness of the affected individuals. This could lead to increased demand by succeeding generations for the usually expensive and complex technical resources needed for such treatment.

### 4.2.3 *Food technology*

The demand for improved techniques of prophylactic treatment will increase. Present techniques of dietary control, for example, have not fully exploited the resources of commercial food technology. More research in the area of food technology and pharmacology relevant to genetic disease is required if the needs of patients are to be met; it is stressed that the number of patients concerned is cumulative and already includes many thousands of individuals.

#### 4.2.4 *Manpower requirements*

The shortage of manpower in medical genetics must be met ; otherwise many or all current and future programmes may be compromised.

It is clear that the medical geneticists and other professional health personnel now available cannot meet all the needs of the patient with genetic disease, particularly those needs that require personal contact, easy communication, and trust between persons. Auxiliary health personnel can already perform these functions effectively in the team approach to the treatment of hereditary disease,<sup>1</sup> and they may be able to collaborate usefully with medical geneticists in other aspects of prevention, treatment, and rehabilitation. The development of new career groups can also be anticipated.

It has been estimated that to meet the genetic health needs of the mid-1980s in North America one person with professional training in medical genetics will be required for every 200 000 persons.

#### 4.2.5 *Resources for rehabilitation*

In the context of this report, rehabilitation is considered to mean the successful adaptation of the patient in his own community. Treatment that deprives the patient of essential faculties (e.g., loss of sight after surgical treatment of retinoblastoma) is far from ideal and rehabilitation is obviously compromised. Treatment that compels the patient to depend on special resources limits his freedom to some extent. Strong dependency on mechanical facilities (e.g., renal dialysis equipment) compromises rehabilitation ; but dependency on a diet or an appliance (such as a hearing aid) need not be a cause of significant disability if the environmental adaptation is obtained at minimal personal and economic cost. Psychological dependencies also require consideration in the rehabilitation process.

#### 4.2.6 *Genetic registries*

Genetic registries can serve many useful purposes in the diagnosis, treatment, and prevention of genetic disease. They differ from conventional disease registries in that they contain identifying information on unaffected relatives as well as on the probands. If the registries are linked to vital statistical records or some other suitable population base, they can provide disease incidence figures suitable for monitoring secular trends and for planning health care needs. Registries may be concerned with a specific disease, a group of diseases, or genetic conditions in general.

Public health officials are already deeply involved in providing services for individuals with genetic defects. In many areas, public health depart-

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<sup>1</sup> Clow, C. L., Reade, T. M. & Scriver, C. R. (1971) Management of hereditary metabolic disease: the role of allied health personnel. *New Engl. J. Med.*, **284**, 1292-1298.

ments are responsible for the administration of genetic screening programmes, for the operation of special educational facilities for the deaf, blind, or mentally retarded, and for the management of various rehabilitation programmes for the physically handicapped. Genetic diseases account for a substantial proportion of the recipients of these services. The incidence at birth of congenital deafness, for example, is one per thousand and of these cases more than 50% are genetic in etiology. In general, however, little use is made of genetic techniques in meeting public health responsibilities to these patients.

The development of a family-oriented genetic registry is a logical first step in the creation of a system for providing counselling, special diagnostic services, treatment, and long-term follow-up for patients with genetic disease.

Fears have been expressed that computerized data banks might be misused in such a way as to threaten the privacy of the individual. The Scientific Group is convinced that genetic registries can be designed and used in ways that will contribute to the diagnosis and prevention of genetic disease without endangering individual rights.

## **5. CONSEQUENCES OF TREATMENT AND PREVENTION OF GENETIC DISORDERS AT THE POPULATION LEVEL**

Medical treatment of hereditary disease and possible strategies for the prevention of genetic defects may be viewed as a form of genetic selection. Treatment, cure, or prevention tends either to remove or to reinforce "natural" selection, which acts against the trait to prevent transmission of the mutant gene by the affected individual to future generations.

### **5.1 Population effects of treatment (relaxed selection)**

The genetic effect of treatment is to remove or relax natural selection. The consequences differ according to the mode of inheritance (see graph in Annex 3).

#### *5.1.1 Recessive traits*

If affected homozygotes for a rare, lethal genetic trait become fully fertile as a consequence of medical therapy, there will be a gradual increase in the frequency of the mutant gene in subsequent generations; this increase will be equal to the mutation rate. For example, from an initial gene frequency of 0.01, 100 generations of completely relaxed selection against a lethal recessive trait would be required to double the gene frequency, assuming a mutation rate of  $10^{-4}$ . Doubling of the gene frequency would in turn lead to a fourfold increase in the frequency of the trait. The change

in disease frequency is slow because the rarer the recessive trait, the greater will be the proportion of abnormal genes that are carried by heterozygotes in the population. The rarer the recessive trait the fewer will be the genes exposed to selection and consequently the smaller will be the effect of complete relaxation of this selection. As stated in section 2.2.3 (1) (last paragraph) and section 4.2.2 (1), maternal effects can limit the social benefits of disease treatment if they lead to the birth of defective offspring in the subsequent generation.

#### 5.1.2 *Dominant traits*

If individuals who have a lethal dominant trait become fully fertile as a consequence of medical therapy, there will be an approximately linear increase in the frequency of the trait in subsequent generations. Thus, a trait with an initial frequency of 0.0001 would increase to a frequency of 0.0086 after 100 generations of relaxed selection, assuming a mutation rate of  $5 \times 10^{-5}$ . The immediate effect in the first generation after the onset of completely relaxed selection would be a doubling of the disease incidence. Thus, the genetic consequences of the treatment of dominant traits are much more disturbing than the results of treating recessive traits. In the case of retinoblastoma, for example, the advent of life-saving treatment by surgery or irradiation has led to a measurable increase in the proportion of familial cases. Formerly, the vast majority of cases were sporadic, representing the occurrence of new mutations. Now, however, the affected children of treated parents are beginning to make a much more significant contribution to the population of patients with retinoblastoma. Usually, however, the advisability of applying a therapeutic measure will be judged much more by the quality or efficacy of the cure than by the theoretical effect on gene frequency.

#### 5.1.3 *Sex-linked traits*

At equilibrium, one-third of all affected males with a lethal recessive sex-linked trait represent new mutations. If selection is relaxed, there will be a moderately rapid increase in the frequency of affected males. Because males do not contribute X chromosomes to their sons, the immediate effects of relaxed selection on disease frequency will be delayed for one generation. However, in about 4 generations the incidence of the disease would double.

#### 5.1.4 *Multifactorial traits*

The theoretical effect of relaxed selection for multifactorial traits is more difficult to predict because the long-term increase in incidence would depend upon the extent to which additive genes determine the trait, and the proportionate contribution of these genes would be expected to change if relaxed selection continued over many generations. However, empirical observation indicates, for example, that the incidence of pyloric stenosis in the offspring

of treated patients is about 5%. The congenital heart diseases are another example of a group of disorders in which modern surgical treatment has profoundly affected survival. Congenital heart disease is etiologically heterogeneous and includes several single-gene syndromes in addition to a large multifactorial component. The incidence of affected children among the offspring of the now numerous survivors of cardiac surgery is approximately 3% in comparison with an incidence at birth of about 6 per thousand in the general population. The incidence of affected offspring among surgically treated patients with myelomeningocele is not yet known, but is also likely to be of the order of 3-4%. Thus it may be anticipated that over the next few generations the incidence of these multifactorial traits will increase by 3-5% per generation, provided that there is no change in the environmental factors contributing to the disease.

#### 5.1.5 *Cytogenetic disorders*

No treatments that significantly raise the reproductive fitness of patients with chromosomal disorders are at present available. Only about a dozen children are reported to have been born to women with Down's syndrome. Individuals with the XXY and XO genotypes are sterile. In general, subjects with the XXX and XYY genotypes have only genetically normal children.

About a third of the children born to women with Down's syndrome have also had Down's syndrome. If some treatment should be found that would raise their chances of marriage and reproduction to normal, therefore, this might lead to at least a 15% increase in the birth frequency of the condition. However, prenatal screening would offer such patients the opportunity of having only unaffected children.

#### 5.2 **Population effects of prevention of mutant genotypes**

It is most improbable, however, that any substantial increase in birth frequency from relaxed selection will take place. Appropriate counter-measures are available, and it is likely that the prevention of the birth of individuals with mutant phenotypes, by genetic counselling and by prenatal diagnosis with selective termination of pregnancy, will lead to a substantial reduction in the frequency of genetic disease.

For serious genetic disorders that are already incompatible with reproduction, selective termination would result in no change in the existing balance between selection and mutation. Less severe traits in which reproduction is possible, would become equivalent to genetic lethals by selective termination. Genetic counselling, urging couples to total abstinence from reproduction, would be a slightly more effective procedure for recessive traits, because prenatal diagnosis with selective termination of pregnancy would still permit parents to contribute abnormal genes to the next genera-

tion through heterozygous offspring. The proportion of cases of a recessive trait that could be prevented either by counselling or by prenatal diagnosis after the birth of an affected proband depends upon the distribution of family size in the population. Reduction of the mean family size, and of the variance of family size, increases the proportion of families with only one affected child and therefore reduces the opportunity to prevent recurrence by counselling. The current distribution of family sizes in the USA would permit a reduction of approximately 15% in the incidence of affected homozygotes, assuming that all recurrent cases in a sibship were prevented. Further reductions would require reliable tests for the detection of heterozygotes. A modest additional reduction could then be achieved by screening relatives of affected probands. Application of heterozygote screening tests to the general population is probably not justified for rare recessive traits. In the absence of an affected proband there may be considerable uncertainty as to the homozygous phenotype for the particular allele in question, because of the high degree of genetic heterogeneity now known to exist in man.

There would seem to be no scientific or public health justification for artificial prenatal selection against heterozygous carriers of recessive traits, even if reliable testing procedures can be devised for their detection. In the case of rare recessive genes, artificial selection against heterozygotes would be folly, since every zygote is estimated to carry 1 or 2 deleterious recessive genes.

### 5.3 Population effects of selection-dependent polymorphisms

Several polymorphic genetic diseases are maintained at a relatively high frequency in the population because of a selective advantage of the heterozygote. Cure of the homozygous state will result in an increase in the gene frequency unless there is a concomitant loss of the selective advantage of the heterozygote. In the case of sickle-cell anaemia and  $\beta$ -thalassaemia, the advantage of the heterozygote may be converted to a slight disadvantage in non-malarious environments, and treatment of the disease would not prevent a slow decline in gene frequency.

The development of an effective prenatal diagnostic test for the affected homozygote, if coupled with screening to detect all heterozygous carriers in the population, could lead to virtual eradication of the disease concerned. In the absence of suitable diagnostic tests, disassortative mating would provide an alternative genetic strategy. If matings between heterozygotes were completely avoided, the incidence of affected individuals would fall to zero. If this were done for heterozygotes for sickle-cell anaemia, in a non-malarious environment there would be a negligible increase in the gene frequency in response to mutation, while with continued selective advantage in a malarious environment the gene frequency would rise. In a population

with a sickle-cell trait frequency of 20%, heterozygotes would experience a 20% reduction in their pool of potential marriage partners, while for normal homozygotes there would be no such reduction. This, in itself, could lead to a somewhat lowered average reproductive fitness which would lower the frequency of the gene.

There are many practical difficulties in implementing a population programme of this sort. In an ethnically heterogeneous population, proponents of mass screening may be accused of racism. It would be necessary to achieve a high rate of cooperation, but in a way that is not prejudicial to couples who choose not to participate.

## 6. PROSPECTS FOR THE NEAR FUTURE

Consideration is given in this section to techniques that are now in various stages of development and may soon be suitable for use in the prevention and treatment of genetic disorders.

### 6.1 Epidemiology

(1) The development of computerized genetic registers, and their linkage to national health statistics, should improve the detection of relatives who require genetic counselling, such as heterozygous carriers of sex-linked traits or balanced translocations, and should facilitate the recall of these patients for counselling just before the reproductive period.

(2) Improved identification of environmental agents that cause mutation, particularly chemical mutagens, may provide an opportunity to reduce the mutation rate below the present level.

(3) The advance determination of sex by the separation of X-bearing and Y-bearing sperms has been attempted for many years. Should a method be found, it would enable individuals who have been successfully treated for X-linked conditions to have only male children who would not then receive the mutant gene.

(4) Epidemiological studies may be able to elucidate the principal environmental components of some of the common multifactorial conditions, and so permit a substantial reduction in their birth frequency.

### 6.2 Prevention

The use of AID is already an accepted technique where both parents are heterozygous for the same mutant gene. As an alternative, some couples may prefer the intrauterine fostering of a blastocyst produced by *in vitro*

fertilization, where both sperm and ovum are donated. Conversely, where a mother has a genetic condition likely to cause intrauterine damage to a fetus, surrogate motherhood, i.e., the transfer of the blastocyst to a volunteer host mother, may become an acceptable practice.

### 6.3 Treatment

#### 6.3.1 *Genetic heterogeneity*

It is already recognized that many disorders with superficially similar phenotype are genetically heterogeneous. The further resolution of such heterogeneity is likely to improve specific methods of treatment.

#### 6.3.2 *Enzyme replacement*

Direct enzyme replacement may become possible in many diseases as a result of current *in vitro* studies with tissue culture systems and organ transplants.

#### 6.3.3 *Directed gene change*

Transduction of mutant cells *in vitro* by virus carrying normal genetic information, followed by implantation of these cells into the host, or the direct application of such methods to the patient, may soon be used in the treatment of certain genetic diseases. These techniques are not without potential hazards.

#### 6.3.4 *Augmentation of cellular enzyme activity*

Pharmacological induction of enzyme activity has been used to augment the activity of some microsomal enzymes (e.g., phenobarbital and steroid stimulation of hepatic conjugating systems). Further work may introduce additional opportunities for this therapeutic approach.

## 7. RECOMMENDATIONS

Many recommendations are contained in the body of this report. The Group feels that special attention should also be given to the activities outlined below.

### 7.1 Medical genetics centres

It is recommended that medical genetics services, including counselling clinics, be provided at each medical school and other major medical centres.

The head of the counselling clinic should be trained in medicine as well as in human genetics. The supporting staff should include other professional

personnel, together with auxiliary health workers with experience in interviewing, family visiting, and the searching and maintenance of records.

There should be access to appropriate clinical and laboratory diagnostic facilities, including cytogenetics, biochemical and other consultative services if these are not provided in the department.

The existence and role of these clinics should be made known to all physicians in the area, whether in private practice or engaged in community health programmes. In particular, there should be close collaboration with the doctors in charge of family planning clinics.

Where suitable personnel are not available, arrangements should be made for the training of physicians, laboratory technicians, and auxiliary health workers.

## **7.2 Education**

To facilitate the effective use of genetic counselling services, increased efforts should be made to educate physicians and the general public, and medical students and schoolchildren in particular, about the principles of genetics and their relevance to human welfare.

## **7.3 Prenatal diagnosis**

While more research is needed into the risks of prenatal diagnosis, there is no doubt that this technique will prove a valuable adjunct to genetic counselling by permitting high-risk couples to have only unaffected offspring. It is recommended that provision be made, in association with genetic clinics, for a considerable increase in the obstetrical and laboratory facilities needed for this procedure.

## **7.4 Registries**

It is recommended that medical genetics centres should set up registries of genetically determined disorders, so that genetic counselling can be offered to all who would benefit by it. Physicians in medical genetics centres should be ready to exchange information, with the usual safeguards of confidentiality, whenever they obtain information about a person at risk near another clinic. The data held in these registries should be linked with a computerized health record linkage system where available, using a uniform system of nosology.

## **7.5 Research**

Apart from the obvious need for research into the etiology, pathogenesis, and treatment of genetic diseases, it is recommended that special attention be paid to the following areas :

- (1) techniques of prenatal diagnosis, especially methods of visualizing and obtaining micro amounts of blood from the fetus ;
  - (2) follow-up of children born after amniocentesis to assess the long-term effects of this procedure, if any ; the continued development of new and improved techniques for the preclinical detection of individuals with genetic diseases ;
  - (3) pilot studies of population screening for heterozygous carriers of specific mutant genes in regions where they are frequent : these studies should include an investigation of the best ways of achieving public understanding and support, of providing suitable counselling without imposing psychological stress on individuals found to be carriers, and of assessing the effect on mating patterns and disease frequency ;
  - (4) epidemiological studies on changes in the frequency of genetic diseases following the introduction of counselling services and new treatments ;
  - (5) studies on the effects on the fetus of inborn errors of metabolism in the mother ;
  - (6) identification of environmental agents that increase or reduce the manifestation rate of genotypes predisposing to multifactorial disorders ;
  - (7) identification and monitoring of environmental pollutants, food additives, and drugs that might increase mutation ;
  - (8) development of methods to control expressed germinal and somatic mutation rates.
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**Annex 1****FREQUENCY OF GENETIC DISORDERS**

Some indication of the case load of genetic disease likely to be found in the community is required in order to plan the deployment of resources for prevention, treatment, and rehabilitation. It is assumed that most patients with disease of genetic origin come to attention either directly or indirectly through the hospital or through screening programmes; but however they come to attention, they may be referred for further diagnosis, counselling, and treatment. Data currently available on the frequency of genetically determined illness are presented in this annex (see Tables 1-4).

The tables do not indicate the anticipated load of patients with multi-factorial disease appearing in later life and thus not identifiable at birth. For example, a strong genetic component exists in mental illness and mental retardation, and patients with these conditions occupy half of all hospital beds in northern hemisphere communities: diabetes mellitus or prediabetes is present in about 2% of the total population in communities of western European origin. Finally, genetic factors account for about 80% of the causes of blindness in nontropical countries and for about 70% of childhood deafness.

**Data from paediatric hospitals**

Diagnoses on discharge from a paediatric hospital can be assigned to 1 of 4 categories: genetic disorders, congenital malformations, unknown, and non-genetic disorders. The term "genetic disorder" comprises chromosomal aberrations and those conditions listed by McKusick;<sup>1</sup> "congenital malformations" includes all diagnoses listed in the classification of Hay & Tonascia;<sup>2</sup> "unknown" refers to conditions not clearly classified but about one-third of which may possibly be hereditary conditions.

Table 1 presents data on the frequency of genetic disease among children admitted to a paediatric hospital in Montreal, Canada. The data cover 12 800 patients between the ages of 1 day and 18 years, admitted during the period from May 1969 to May 1970.

The corresponding data for patients in older age groups are not yet available, but it can be anticipated that they will show a genetic component of at least a similar order of magnitude.

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<sup>1</sup> McKusick, V. A. (1968) *Mendelian inheritance in man*, 2nd ed., Baltimore, Johns Hopkins.

<sup>2</sup> Hay, S. A. & Tonascia, S. (1968) *A classification of congenital malformations*, San Francisco, US Public Health Service, Dental Health Center.

TABLE 1. FREQUENCY OF GENETIC DISORDERS AMONG PATIENTS ADMITTED TO A PAEDIATRIC HOSPITAL, MONTREAL, 1969-1970

Condition requiring hospitalization	Percentage of all admissions	
Genetic disorders :		
Autosomal recessive	2.0	} 11.0
Autosomal dominant	2.0	
X-linked	2.7	
Chromosomal	0.4	
Multifactorial	3.9	
Congenital malformations		18.4
Unknown		6.9
Non-genetic disorders		63.7
		<u>100.0</u>

TABLE 2. APPROXIMATE FREQUENCY OF SOME COMMON MULTIFACTORIAL MALFORMATIONS

Condition	Frequency per 100 000 births	Location
Anencephaly	400	Northern Ireland
	200	England
	80	Japan
	50	West Africa
Myelomeningocele	250	England
	30	Japan
	20	Nigeria
Heart malformation (all types)	600	England, N. America, Sweden
Cleft lip (without or without cleft palate)	300	Japan
	100	England, Denmark, N. America
	40	Nigeria
Congenital dislocation of hip (late diagnosis)	400	Norway (Lapps)
	100	Sweden, England
(early diagnosis)	400	Sweden, Scotland
Talipes equinovarus	400	New Zealand (Maoris)
	100	England, N. America, Japan, Nigeria
Pyloric stenosis	300	England, Sweden

TABLE 3. FREQUENCY OF SOME FORMS OF HEREDITARY METABOLIC DISEASE

Disorder	Apparent frequency per 100 000 live births	Region or population group
Maple syrup urine disease	0.3	General
Classical phenylketonuria	7.0	North-eastern USA and eastern Canada
Benign hyperphenylalaninaemia	3.0	
Homocystinuria	3-8.0	
Cystinuria	7.0	
Histidinaemia	6.0	
Arginosuccinicaciduria	0.5	
Galactosaemia	3.0	
	0.4	New York State, USA
		Massachusetts, USA
Hereditary tyrosinaemia	30.0	Quebec isolate, Canada
	0.4	North-eastern USA and eastern Canada
Tay-Sachs disease	30.0	Ashkenazi Jews
Cystic fibrosis	50.0	Europeans

TABLE 4. APPROXIMATE FREQUENCY OF SOME CHROMOSOMAL ABERRATIONS \*

Condition	Frequency per 100 000 births
Down's syndrome (general)	140
Down's syndrome (where mother is over 40 years of age)	1 000
Edward's syndrome (trisomy 18)	20
Patau's syndrome (trisomy 13)	10
XXX genotype	50
XXY genotype (Klinefelter's syndrome)	80
XYY genotype	100
XO genotype (Turner's syndrome)	3

\* Estimates for various parts of the world are similar. The data in this table represent studies in Australia, Canada, India, Mexico, the Netherlands, Poland, Sweden, the United Kingdom, the USA, and the USSR.

### Data from mass screening programmes

Data for empirical frequencies of several forms of genetic disease are now available from mass screening programmes in various regions of the world. The frequency of any given trait may vary from one population to another. The following estimates are given only as a general indication of the anticipated case loads.

Some examples of the case load at birth of multifactorial genetic disorders are given in Table 2. Estimates of case frequency in later life are not given, since in most instances this will vary in accordance with the factors discussed in section 2.3 (see p. 12).

The approximate case load of some rare autosomal recessive traits in the category of "hereditary metabolic disease" is shown in Table 3. If the trait is eligible for prophylactic treatment, these diseases become cumulative.

The approximate case load of chromosomal aberrations is illustrated by some examples in Table 4. The estimates are for both sexes, at birth, in the world as a whole.

### Mortality data

The case load of genetically determined disease severe enough to terminate in death has been specifically examined by Carter<sup>1</sup> in autopsy records from a London children's hospital, and by Roberts et al.<sup>2</sup> in records of all deaths in the Newcastle upon Tyne region of England. These estimates suggest that not less than 11% of paediatric deaths can be attributed to genetic disease, while at least another 19% result from congenital malformations.

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<sup>1</sup> Carter, C. O. (1956) Changing patterns in the causes of death at the Hospital for Sick Children. *Gt Ormond Str. J.*, **11**, 65-68.

<sup>2</sup> Roberts, D. F., Chavey, J. & Court, S. T. M. (1970) The genetic component in child mortality. *Arch. Dis. Childh.*, **45**, 33-38.

## Annex 2

**HEREDITARY DISEASES ELIGIBLE FOR PRENATAL  
DIAGNOSIS \***

All the diseases in the following list can now be diagnosed prenatally. Those in italic type have actually been diagnosed *in utero*.

**Disorders of amino acid metabolism**

Arginosuccinicaciduria  
Cystinosis<sup>1</sup>  
Homocystinuria<sup>1</sup>  
Hyperammonaemia (OTC deficiency)<sup>1</sup>  
Hypervalinaemia  
*Maple syrup urine disease*<sup>1</sup>  
*Methylmalonic aciduria*  
Ornithine- $\alpha$ -ketoacid transaminase deficiency

**Disorders of carbohydrate metabolism**

*Glycogen storage disease (type II)*  
Glycogen storage disease (type III)  
Glycogen storage disease (type IV)  
Galactosaemia<sup>1</sup>  
Mannosidosis  
G6PD deficiency<sup>1</sup>

**Disorders of lipid metabolism**

Gaucher's disease  
Generalized gangliosidosis  
 $\beta$ -galactosidase deficiency<sup>1</sup>  
*Tay-Sachs disease* (hexosaminidase-A deficiency)  
*Sandhoff's disease* (hexosaminidase- (A + B) deficiency)

**Metachromatic leukodystrophy**

Niemann-Pick disease  
Refsum's disease

**Mucopolysaccharidoses**

*Hunter's syndrome*  
*Hurler's syndrome*

**Miscellaneous inherited traits**

Adrenogenital syndrome<sup>1</sup>  
Lesch-Nyhan syndrome  
Lysosomal acid phosphatase deficiency  
Xeroderma pigmentosum  
Acatalasaemia  
Chediak-Higashi syndrome  
Congenital erythropoietic porphyria  
Cystic fibrosis<sup>1</sup>  
I-cell disease  
Oroticaciduria<sup>1</sup>  
Sickle cell disease

**Chromosomal aberrations**

Many: about 1 liveborn child in 200 has a chromosomal aberration; the frequency of affected offspring increases with higher maternal age.

In addition, the following hereditary diseases are likely to become eligible for prenatal diagnostic procedures in the near future:

\* Adapted from Milunsky, A., Littlefield, J. W., Kanfer, J. M., Kolodny, E. M., Shih, V. E. & Atkins, L. (1970) Prenatal genetic diagnosis. *New Engl. J. Med.*, **283**, 1370, 1441, 1498.

<sup>1</sup> Since these conditions are known to be genetically heterogeneous, particular care must be taken in their diagnosis.

**Disorders of amino acid metabolism**

Citrullinaemia  
Hyperlysinaemia <sup>1</sup>

**Disorders of carbohydrate metabolism**

Fucosidosis  
Lacticacidosis (pyruvate decarboxylase  
deficiency) <sup>1</sup>

**Disorders of lipid metabolism**

Fabry's disease  
Maroteaux-Lamy syndrome  
Morquio's syndrome  
Sanfilippo's syndrome  
Scheie's syndrome

**Congenital malformations**

Those recognizable by ultrasound techniques or amnioscopy

Diseases for which the diagnostic criteria are inadequate, or for which there is no clinical or medical justification for prenatal diagnosis, are not considered in this annex.

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<sup>1</sup> Since these conditions are known to be genetically heterogeneous, particular care must be taken in their diagnosis.

## Annex 3

**APPROXIMATE PROPORTION OF GENETIC TRAITS WITH  
SIGNIFICANT EFFECT ON GENETIC FITNESS**

An estimate of the maximum possible impact of relaxed selection on the total burden of recognized human genetic disease is presented in the accompanying table. The estimate of the load of multifactorial diseases is derived from the approximate incidence of three multifactorial traits that have already been profoundly influenced by therapy, i.e., congenital heart disease, spina bifida, and pyloric stenosis (see section 5.1.4). Restoration of full fertility to all these patients (which is not yet possible for spina bifida) would result in a 3-5% increase in the traits per generation, or a doubling time of 14-23 generations.

Mode of inheritance	Approximate no. of recognized conditions		Approximate total frequency	Approximate doubling time in generations <sup>a</sup>
	Lethal	Total		
Autosomal dominant	200	800	0.002	1
Autosomal recessive	300	600	0.003	50
Sex-linked	100	120	0.001	4
Multifactorial (major malformations)	3	12	0.012	14-23
Total			0.018	6-7

<sup>a</sup> Assuming that reproductive fitness is raised from 0 to 1.

The estimates for Mendelian conditions are derived from the approximate proportion of traits listed by McKusick<sup>1</sup> that have a major effect on survival and reproduction, under the assumption that each deleterious trait has a frequency of  $10^{-5}$ . This set of assumptions may not apply to all populations. Since not all of these traits are genetic lethals, and it is unlikely that effective treatments will be developed for every trait in the near future, the data provide a maximum estimate of the effect of relaxed selection.

<sup>1</sup> McKusick, V.A. (1968) *Mendelian inheritance in man*, 2nd ed., Baltimore, Johns Hopkins.

The last column gives a weighted mean of the effects of treatment on Mendelian and multifactorial traits. Although the load of individual dominant traits could double in a single generation, the total load of genetic disease is not likely to double in less than 6–7 generations even if effective treatments for all traits are found immediately.

The doubling time in generations for pure genetic traits, assuming that treatment permitting the reproduction of affected persons becomes possible, is shown in the accompanying graph.

TIME IN GENERATIONS NECESSARY TO DOUBLE THE FREQUENCY OF A LETHAL GENE, IF REPRODUCTION OF AFFECTED PERSONS BECOMES POSSIBLE, AT MUTATION RATES OF THE ORDER OF  $10^{-4}$

