Prevention and Control of Genetic Disease

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Since the turn of the last century there has been a gradual change in the pattern of disease. With advances in medicine and surgery and the introduction of antibiotics, nutritional deficiencies and infectious diseases have become less common. Their place, as causes of morbidity and mortality, has been taken by disorders that are at least in part genetic in origin. For example, in a recent survey of childhood deaths in hospital in Newcastle-upon-Tyne, no less than 42 per cent could be attributed to disorders that were largely or even entirely genetically determined (Roberts et al., 1970). Lederberg has estimated that 25 per cent of our health burden is of genetic origin and he has suggested that the genetic legacy of the species will, in the near future, compete only with traumatic accidents as the major factor in health.

Whereas in the past the prevention of disease in the population involved public health measures and the traditional skills of medicine, the prevention of genetic disease requires a different approach and demands different skills. The prevention of genetic disease involves, firstly, the ascertainment of individuals in the population who are at risk of having affected children; secondly, the provision of genetic counselling for those found to be at risk. Finally, antenatal diagnosis with selective abortion of affected fetuses may be offered in the case of chromosomal and certain biochemical disorders.

Ascertainment of Those at Risk

There are a number of ways of ascertaining which individuals are at high risk (greater than 1 in 10) of having a child with a serious genetic disorder. At present it is usually the result of routine diagnosis when an individual is found to have a disorder that is known to be genetic, and this clearly depends on the awareness of the problem by the medical practitioner. Of some 800 families seen in our genetic clinic over a number of years, only about 15 per cent of individuals found to be at high risk of having a child with a serious genetic disorder were referred specifically for genetic counselling. Other methods of detecting individuals at risk include population screening (for example, for phenylketonuria) and family screening (Fig. 1). The latter should be a natural consequence of detecting a genetic disorder in a family; e.g. in the case of
Duchenne muscular dystrophy, the carrier status of female relatives can be determined from serum creatine kinase estimations.

Although the detection of families with serious genetic disorders is usually achieved through general practitioners and hospital consultants, additional information might be gained from record linkage with public health records (for example, school medical officers' reports) and statutory registers such as the Disabled Register.

**GENETIC REGISTER SYSTEM**

Having ascertained families in the population with genetic disease, information on individuals found to be at high risk in these families may have to be stored for future reference. Because of the magnitude of the problem, the need for confidentiality, frequent up-dating of family information and the follow-up of individuals found to be at risk, a computerised genetic register system with linkage to other register systems might be valuable. To be effective, such a system would have to be organised on a national basis. The organisation of a register system is given in Fig. 2. Such a system would be of value both in the tracing and follow-up of those at risk of having affected children, but it might also be of value in indicating individuals with inherited susceptibilities to drugs and for detecting and eradicating life-threatening complications of genetic disease such as intestinal malignancy in polyposis coli (McKusick, 1969). However, the main function of a genetic register system should be the prevention of genetic disease. For this reason the register being developed in this Department is referred to by the acronym 'RAPID' (Register for the Ascertainment and Prevention of Inherited Disease). The programme, details of which are available (Moores, 1972), is in IMP and may be modified to other computer languages.

Because of the need to maintain strict confidentiality of the information in the register a number of security checks have been incorporated. Each family, and all individuals at risk in the family, are allotted code numbers which are
used in all subsequent manipulations of the data. A master key is kept by the physician and statistician who are responsible for the register. Access to the system by anyone working with the register is only possible when a valid password ‘A’ has been used (Fig. 3). One may then directly choose to amend the file data. Since this does not involve data retrieval, no further checks of the subsystem are necessary. If, however, the operator wishes to retrieve data the request must first be checked for its validity, i.e. correct family names, numbers and disease code, etc. A legitimate user may on occasions make an error, and for this reason an error count is introduced into the system. Finally, a second password ‘B’ is needed. This allows data to be retrieved at different levels depending on the individual’s password. For example, the physician dealing with a family has access to all the genetic and medical information on the individuals in the family. On the other hand, a field worker who is only concerned with tracing relatives may retrieve only pedigree data.

Such a system of checks might be considered excessively elaborate but we feel it is justified as information about inherited disease is more subject to possible misuse than purely clinical information. For example, persons at risk from certain genetic disorders, though perfectly healthy, might find themselves at a disadvantage if a prospective employer were aware of their liability. Information about any individual in the register is released only to physicians who are directly involved in the management of the patient and his family.

The most difficult problem in such a register system is the development of procedures for contacting individuals who are considered to be at high risk.
but were not referred to the investigator. The procedure adopted in this Department is that the permission of the patient first contacted (index case) must be obtained before other family members are approached. When this permission is given the relatives at risk are contacted not directly but through their general practitioner (whose name and address can be obtained, for example, through the Executive Council). This is considered important, as there may be factors unknown to the geneticist or index patient that might make it imprudent to contact a particular relative. The problem of whether parents should be told of their risks even when this information has not been requested has

Fig. 3. Simplified outline of the RAPID system.
recently been considered at length both from the scientific (Littlefield, 1972) and ethical (Lappe et al., 1972) points of view. The author's feeling is that parents ought to know these risks in situations in which prevention is possible.

**Genetic Counselling**

Such a system can be of value only if individuals at risk understand and react responsibly to genetic counselling. The comprehension of genetic advice is difficult to assess, but the results of two recent studies suggest that the majority of couples do understand and remember the risks (Carter et al., 1971; Emery et al., 1973), but this has not been so in other studies (Leonard et al., 1972). However, in the latter study, advice was provided by a number of agencies presumably not all with the same effectiveness. Ways in which the comprehension of genetic advice might be improved include a second clinic visit, when information given at the first visit can be reinforced, a written summary of the advice given, and a follow-up discussion in appropriate cases some 6 to 12 months later. The amount and nature of the information imparted should obviously be geared to the educational background of the individual. For this reason it is sometimes better to emphasise risks in general terms rather than attempt to explain mathematical probabilities.

In assessing the response to genetic counselling it is difficult to compare the results of different studies which often reflect the personality and perhaps the prejudices of the particular counsellor. In Table 1, a comparison has been made between the effects of genetic counselling in Duchenne muscular dystrophy, where the disease has a protracted and downhill course over many years, and therefore presents a heavy burden on the family, and other serious disorders where the burden might be considered less because the disorder in question resulted in stillbirth or death in infancy. The results suggest that the heavier the burden of the disease on the family, fewer at high risk (greater than 1 in 10) are undeterred from further pregnancies, while more of those at low risk (less than 1 in 20) are unreassured and limit their families. Of the 10 couples

| High risk undeterred (%) | Low risk unreassured (%) |
|--------------------------|-------------------------|
| Duchenne muscular dystrophy | 2/40 (5%) | 1/6 (17%) |
| Other disorders | 10/55 (18%) | 1/30 (3%) |
in the high-risk group for disorders other than Duchenne muscular dystrophy who planned further pregnancies, 3 apparently ignored the risks completely (one mother has since been sterilised), 2 planned further pregnancies because they were unable to adopt a child, and one mother chose antenatal diagnosis with selective abortion. In 4 other cases the parents planned pregnancies because they had no living children and considered the burden to the family of an affected child would be of relatively short duration because the disorder in question usually resulted in stillbirth or death in infancy (Emery et al., 1973). Parents seem to be influenced as much by the possible burden of an affected child on the family as they are by the actual risks of recurrence.

ANTENATAL DIAGNOSIS
Family limitation is not the only course of action open to parents found to be at high risk of having a child with a serious genetic disorder. Other possibilities include artificial insemination by donor (if the father is affected with a dominant disorder, or if both parents carry a gene for a rare recessive disorder) and more recently, antenatal diagnosis with selective abortion of affected fetuses (Emery, 1973). From the study of cells present in amniotic fluid obtained by transabdominal amniocentesis carried out at about the 14th week of gestation it is possible to sex the fetus. This is useful in the case of X-linked disorders that cannot yet be diagnosed in utero (e.g. Duchenne muscular dystrophy). A known carrier may decide to have her pregnancy terminated if the fetus is a male because there is a 1 in 2 chance of the fetus being affected. In this way a carrier mother can be guaranteed a daughter who will not be affected (though she might prove to be a carrier). In the case of X-linked disorders where males can survive and have children (e.g. haemophilia), selective abortion of female fetuses may be accepted because all the daughters of an affected male will be carriers, but all his sons will be normal. Selective abortion of female fetuses might also be considered in certain autosomal recessive and X-linked dominant disorders in which affected males die in utero and spontaneously abort, but affected females can survive (e.g. incontinentia pigmenti).

Amniotic fluid cells can also be cultured, and in this way it is possible to diagnose chromosomal abnormalities in the fetus. This is particularly valuable in the case of Down's syndrome, as the risk of having an affected child is related to maternal age and rises to about 1 in 50 in mothers over 40. For this reason a policy of screening by amniocentesis all mothers over the age of 40 may become acceptable in the future (Stein et al., 1973). From biochemical studies on cultured amniotic fluid cells it is so far possible to detect about 30 inherited metabolic disorders in utero in early pregnancy (e.g. Tay Sachs' disease, Pompe's disease, Lesch-Nyhan syndrome, galactosaemia, etc.). Finally,
fetoscopy may prove valuable in the antenatal diagnosis of certain congenital malformations not associated with any recognised biochemical or chromosomal abnormality. In autosomal dominant disorders, genetic linkage studies may also prove helpful. For example, the genes for myotonic dystrophy and secretor status are linked and the secretor status of the fetus can be determined from amniotic fluid. In certain families this information could be valuable in predicting whether the fetus had inherited myotonic dystrophy from an affected parent.

Table 2. Indications for antenatal diagnosis (where this is possible) according to the risks of having an affected child

| 1. Risk > 5% |
|--------------|
| (a) Familial chromosomal translocations |
| (b) X-linked recessive disorders |
| (c) Autosomal recessive or X-linked dominant disorders lethal in male |
| (d) Autosomal recessive disorders |
| (e) Autosomal dominant disorders (possible in myotonic dystrophy through linkage with secretor gene) |

| 2. Risk 1–5% |
|--------------|
| (a) Down's syndrome, previous trisomy-21 or maternal age > 35 |
| (b) Certain congenital malformations |

Some of the main indications for amniocentesis according to the risk of having an affected child, are summarised in Table 2. The risks to the mother of amniocentesis carried out in early pregnancy are probably very small. The risks to the fetus have not yet been accurately assessed. In view of this uncertainty, one might hesitate to recommend amniocentesis unless the risk of an abnormal child is greater than, say, 5 per cent, or in exceptional circumstances where maternal anxiety is an overriding consideration.

CONCLUSIONS
We have seen that genetic disorders are beginning to play an increasing role in morbidity and mortality. Their prevention involves ascertaining those at risk of having affected children, providing genetic counselling for prospective parents found to be at risk, and antenatal diagnosis with selective abortion when this is possible. The ascertainment of those at risk depends on the recognition of the problem by members of the medical profession, and could be facilitated by a computerised genetic register system such as RAPID. However, if such a system were to be effective it would have to be organised on a national basis. With regard to genetic counselling, evidence suggests that parents are
influenced as much by the possible burden of an affected child on the family as they are by the actual risks of recurrence, and both aspects of the problem need to be explained to prospective parents. Finally, antenatal diagnosis with selective abortion of affected fetuses offers the possibility of a healthy child in families at risk of having a child with certain chromosomal or inherited biochemical disorders. Through the development of techniques for the antenatal diagnosis of genetic disorders, coupled with genetic counselling, it should be possible to prevent an increasing proportion of genetic disease in the future—a hope which, unlike Keats (*Endymion*) I do not consider to be ‘... beyond the shadow of a dream’.

*This article is based on a paper read at the College Conference on Individual and Geographical Differences in Susceptibility to Disease and Response to Drugs held in Norwich in September 1973.*

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