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PRENATAL DIAGNOSIS AND SELECTIVE ABORTION

Harry Harris
MD, FRCP, FRS
Galton Professor of Human Genetics
University College London
Honorary Director, MRC Human Biochemical Genetics Unit

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I

Introduction

The recent introduction of precise techniques for the prenatal diagnosis of a variety of different genetic defects represents a new departure in medicine. This is not because of the nature of the particular techniques which have been developed to make the diagnoses, but because of the objective at which making the diagnosis is aimed.

In conventional medicine the aim of diagnosis is to enable the patient to be treated most effectively, and if diagnosis should turn out to be one for which no effective treatment is available, then the aim is to ameliorate the patient's condition as far as this is possible.

But the object of prenatal diagnosis of genetic defects is exactly the opposite. The aim is to find out whether the foetus has some defined abnormality which will inevitably lead to the birth of a defective infant and, if so, to abort the foetus.

It is not therefore surprising that the introduction and increasing application of prenatal diagnosis with its corollary, the abortion of defective foetuses, should have generated a considerable amount of discussion and argument.

One of the conditions for which the technique of prenatal diagnosis is particularly suited and to which it is being widely applied is mongolism (Down's syndrome). This is a developmental abnormality which inevitably results in a severe degree of mental retardation, amounting usually to idiocy or imbecility. Furthermore it is by no means uncommon, since about one in every 600–800 new-borns have the abnormality (1), and it is thought to account for some 30 per cent of the severely mentally retarded children in this country (2). A proportion of the affected infants die in childhood, but with the general advances which have taken place in medical care more are surviving and many now live well into adult life. But there is no known way of

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ameliorating the mental defect, so that these patients impose a considerable burden on the families into which they are born and more generally on the health services.

In 1959 a major advance in our understanding of mongolism came with the discovery by Jerome Lejeune and his colleagues in Paris, of the chromosomal basis of this abnormality (3). And this discovery was, in fact, the key element which made possible the introduction of the prenatal diagnosis of mongolism a few years later. But Lejeune himself regards this application of his discovery as unethical and immoral. In a lecture (4) to the American Society of Human Genetics he told his audience that if they proposed to pursue prenatal diagnosis and consequently the abortion of abnormal foetuses on the scale which many of them had advocated, then the famous 'National Institute of Health', their largest and most prestigious centre for biomedical research would need to set up a new institute called the 'National Institute of Death'.

Most human geneticists do not agree with Lejeune's thesis. They consider that it dismisses too easily the welfare of afflicted families and the general social good. But it is not surprising that the topic has generated much discussion and argument about the various ethical issues raised by the introduction of abortion for genetically abnormal foetuses, both with regard to the criteria which should be applied in different types of case, and with regard to wider social questions.

These discussions started among human geneticists because the possibilities for prenatal diagnosis apply particularly to inherited diseases and to other abnormalities of genetic constitution, and because most of the discoveries which have made the procedure possible have come from genetical laboratories. But before long experts from other fields entered the controversies. Obstetricians, of course, were involved because they have to perform the abortion if this is indicated. But experts on public health and social medicine and also on ethics, on theology, on sociology, and on philosophy, have also entered into the arguments. In addition there are the legal experts, who are concerned with the implications of the new abortion laws and who also see a new area of litigation looming up concerned with the legal rights of the foetus and the defective live-born.

Many conferences and symposia have been held in which experts from these various fields have taken part. In addition, numerous articles have appeared in medical and other journals as well as in the popular press. And many fine words have been spilt.

The now quite extensive literature (5), both about the general morality of the procedure and the particular ethical criteria which it is argued ought to apply in specific cases is often very confusing, because of the diversity of the approaches and because of differences in basic assumptions which often appear to underlie the various arguments. It is perhaps noteworthy that the conclusions reached by the different professional ethicists who have been involved in these discussions appear to be just as diverse as those of other people. In general it would seem that these particular ethical issues are more difficult to resolve than those which arise in most other branches of medicine.

The use of particular terms in these discussions and arguments calls for some comment because they are often loaded. For example, the abortion of a genetically abnormal foetus is often referred to as a 'therapeutic abortion'. It has, however, been pointed out by those who are less than enthusiastic about the procedure, that it can hardly be described as 'therapeutic' as far as the foetus is concerned. On the other side there is a preference for using terms such as 'the unborn child' or 'the yet unborn' to refer to the foetus the abortion of which may be under consideration. Such euphemisms tend to blur the basic issues and it seems desirable to try and avoid them, though this is often difficult in this particular field.

In what follows I will use the term 'selective abortion' for abortions carried out specifically because the foetus has been shown to be affected by a particular abnormality, or has a high probability of being affected. Such a term is needed since it is necessary in many contexts to distinguish between abortions carried out for this reason, and the great majority of abortions which are carried out for quite other reasons. I will also distinguish between infants and children on the one hand and foetuses on the other, since in many arguments it is desirable to differentiate clearly between an infant or child after it is born, and

what it is at a much earlier stage of its development. No doubt these terms are still open to criticism, but they seem to me to be the least loaded of the terms which can be conveniently used.

Quite apart from its immediate impact on the practice of medicine, prenatal diagnosis and selective abortion also needs to be looked at in a broader biological context, since the selective elimination of genetically abnormal foetuses can in principle lead to long-term alterations in the genetic make-up of human populations.

The inherited diseases and other genetically determined abnormalities which are present among the living members of our species today can, in general, be attributed to the occurrence of mutational events which occurred in the gonads of single individuals among our ancestors in the past. Some of these mutations no doubt originally occurred many generations ago, but others originated relatively recently and some took place in the germ cells of one or other of the parents of the patient who now shows the abnormality. The incidence of particular genetically determined abnormalities depends on the rates at which different sorts of mutational event occur, on the action of natural selection, and to some extent on chance effects or what is referred to technically as random genetic drift, although the relative importance of this last factor is controversial.

Natural selection acts by reducing or preventing altogether the contribution an individual makes to the next generation. A particular genetic abnormality may result in death in foetal life or in post-natal life before the age of reproduction, so that the genes that individual carries are not passed on to individuals of the next generation. Or the abnormality may affect the individual in such a way that he or she is less likely than other people to marry and have children. Or he or she may be relatively less fertile.

Diagnosis and treatment in conventional medicine can be regarded, in so far as it is applied to genetically determined disorders, as producing a relaxation of the effects of natural selection. This is because it may enable individuals who would previously

have died in early life or have been severely handicapped, to live normal or nearly normal lives and so be more likely to contribute to the next generation. The remarkable progress which has been made in recent years in the treatment of phenylketonuria illustrates the point. Previously most phenylketonurics were mentally retarded to a severe degree and only very rarely had children. Now a new generation of phenylketonurics is growing up on a phenylalanine-restricted diet and although it is perhaps too early yet to judge the final outcome, the great majority of them appear to be intellectually within the normal range and it may be expected that they will eventually marry and contribute their genes to individuals in the next generation. This is a remarkable achievement in a disease which was at one time thought to be therapeutically hopeless, and in which most of the patients were expected to have to live permanently in institutions for the mentally retarded.

It is true, of course, that a specific therapeutic approach such as that which has been so successful in phenylketonuria is at present only available for a very small fraction of all genetically determined abnormalities, and that for many conditions the development of an effective therapy seems very remote. But the general advances in medical and social care in the past few decades have inevitably meant that the life-span and the reproductive ability of many sufferers from inherited abnormalities has been extended from what it once was, and this in itself amounts to a relaxation of natural selection.

Some authors have viewed with considerable alarm the advances in medicine which may be seen as reducing the impact of the force of natural selection. They argue that they must inevitably result, if no other action is taken, in the progressive accumulation of deleterious genes in human populations, so that eventually the species will collapse under the burden of its genetic load. Others, however, have argued that evolutionary progress has always involved changes in the environment, and that advances in medicine and in public health simply represent one of the changes in the human environment which are occurring at the present time. In certain cases genes which in an earlier environment had been deleterious may no longer be so in the new

environment. Furthermore a close examination of the rate of change in gene frequencies which may be plausibly anticipated in specific cases, does not on the whole justify alarmist prognostications or prophecies of doom (6).

However, prenatal diagnosis and therapeutic abortion would appear to act in relation to natural selection in a quite opposite manner to other developments in medicine. This is because the aim is to prevent the further existence of the abnormal foetuses, rather than to ameliorate the disorder. So the general effect is to enforce the operation of natural selection.

In some cases, for example mongolism, the effect in terms of contribution to the next generation is almost negligible, since very few mongol patients have children. But in other cases some resulting changes in the future genetic constitution of the species can be expected. Curiously enough this may not always be in the direction which at first sight might be anticipated, since under certain circumstances selective abortion may actually tend to result in an increase in the incidence of the particular abnormal gene in future generations, rather than the opposite (see Chapter 3, pp. 50–51 and 56).

Despite the remarkable advances in medicine which have taken place in the last few decades, it is perhaps important to emphasize that natural selection continues to play a major role in determining the genetic constitution of the species. Furthermore recent discoveries have made it clear that much of its force operates very early in foetal life. About 15 per cent of all new members of our species who arise by the fertilization of an ovum by a sperm, are thought to die in the early part of pregnancy and to be eliminated by spontaneous abortion. And at least 35 per cent of such foetuses have been found to have chromosomal abnormalities which evidently severely reduce their viability (see Appendix 1). Thus the normal chromosomal constitution of the species which tended in the past to be thought of as a rather stable affair prone only to occasional aberrations, can now be seen as being maintained by an intense pressure of natural selection at an early stage of foetal life, which culls out the aberrations by spontaneous abortion. There is indeed some justification for the statement that 'nature is the greatest abortionist' (7).

So it can perhaps be argued that the elimination by selective abortion of other chromosomal abnormalities which though severe nevertheless allow the foetus to survive to be born, is in essence simply an extension of what nature normally brings about. And in quantitative terms it is only a very small extension (see Appendix 1). In this connection it is of interest to note that recent studies indicate that the mongol infants actually born probably represent only about 35 per cent of all foetuses with a chromosomal constitution characteristic of mongolism (8). The remaining 65 per cent of potential mongol infants are evidently eliminated spontaneously in early pregnancy.

In general the introduction of prenatal diagnosis and selective abortion into medicine has raised a variety of ethical and biological questions which can be expected to have important social implications. But before considering these questions further it is obviously desirable to examine the general scope of the procedure and, in particular, the types of situation to which it can be applied.

2

The scope of prenatal diagnosis

It is perhaps important to emphasize at the outset that prenatal diagnosis is a very recent innovation (1). Its potentialities only became apparent in the middle 1960s, and the following few years saw a series of rapid developments which are indeed still going on. So besides looking at the range of situations to which prenatal diagnosis is presently applicable, it may be worth while trying to speculate a little on how these may be extended in the future.

As a rule it is necessary to obtain a sample of amniotic fluid in early pregnancy. This generally contains enough viable cells derived from the foetus which can be used to set up a tissue culture in which further actively dividing cells are produced. In most cases the diagnosis is made by examining these tissue-cultured cells, which usually have the form of fibroblasts. For some purposes what is required is an analysis of the chromosomes, which is done using appropriate staining techniques on those cells which are in the metaphase stage of cell division. In other cases the diagnosis depends on an enzyme assay or occasionally some other biochemical test carried out on the bulked tissue-cultured cell material. Direct examination of the amniotic fluid cells without tissue culture can sometimes provide information either about the sex of the foetus or about its biochemical status, but generally this, though much quicker, appears to be a less reliable procedure and the tissue-culture technique is preferred. In certain cases, direct estimation of a particular protein or other constituent of the amniotic fluid itself is required (for example, α-foetoprotein for neural tube defects).

Amniocentesis to obtain the sample of amniotic fluid is generally done transabdominally as an out-patient procedure. The timing is critical. The uterus is usually palpable abdominally from about 10 to 12 weeks of gestation onwards. However, the volume of amniotic fluid increases rapidly from an average of about 30 ml

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at 10 weeks to about 750 ml at 15 weeks, and usually the aim is to remove a sample of 10–20 ml. So 15–16 weeks is generally regarded as the optimal time. To delay longer leads increasingly to other problems.

It usually takes 2–3 weeks to grow enough cells in tissue culture to make a satisfactory chromosomal diagnosis. For enzyme assays or other biochemical tests many more cells are required and this may mean prolonging the period of growth in tissue culture to 4–6 weeks or even longer. But since abortion is contemplated if the foetus is found to be abnormal, it is necessary to arrive at the diagnosis by at least 20–22 weeks. Although at present the legal limit for abortion is 28 weeks, most obstetricians would regard it as very undesirable to delay as long as this.

Furthermore although the technical procedures involved in the tissue-culture part of the process have been improved very considerably in the few years in which prenatal diagnosis has been attempted, there is still an area of uncertainty about the optimal conditions required. Not all tissue cultures set up from amniotic cells grow properly, and the success rate even in the most experienced laboratories falls short of 100 per cent. This necessitates repeating the amniocentesis in some cases and of course time is by then beginning to get short.

The reasons for the failure of some cultures from amniotic cells are still obscure and further research into the best culture conditions is required. Certainly the time which may elapse between the amniocentesis in the clinic and the setting up of the culture in the laboratory is important. The shorter the better, and in particular it appears that when samples have to be sent long distances through the post, the probability of a successful culture is less than if the clinic and the laboratory are close together and the delay is minimal. But in some cases it is possible that the cell culture fails to thrive precisely because the foetus is abnormal and the particular defect manifests itself in tissue culture by poor growth. And of course such cases are the ones where the diagnosis is particularly required.

The safety of amniocentesis both for the normal foetus and for the mother is a key element in validating the procedure. On the whole, experience to date indicates that it is a reasonably safe procedure. In perhaps 1–2 per cent of cases the procedure has been

followed by spontaneous abortion or missed abortion in the subsequent weeks of pregnancy. However, it is not yet clear to what extent these effects can be actually attributed to the aminocentesis itself. To find this out involves not only a detailed analysis of each case, but also the careful assembly of data from equivalent pregnancies in which amniocentesis was not carried out. This is not as easy as it might seem because of the inherent difficulties of constructing a control series of pregnancies, which in other respects such as maternal age, social and home background, and nature of medical facilities available to them, are closely comparable with the series of pregnancies which had undergone amniocentesis. The actual procedure adopted in the amniocentesis is also relevant. Most obstetricians regard the localization of the placenta using ultrasound as an essential prerequisite. But this facility is by no means everywhere available.

Follow-up of the normal infants born to mothers who had amniocentesis, and a comparison with appropriate controls is also necessary. The whole procedure is much too recent for any extensive results to have yet emerged from such studies. It does not appear that there is any gross increase in the incidence of congenital abnormalities over that which would in any case be expected in a comparable group. But again, more detailed and extensive follow-ups with appropriate controls will be required before it can be said with certainty that the incidence of malformations is not at all increased above the ordinary incidence expected (about 2 per cent) according to what grading of malformation is adopted. Similarly, it is not yet possible to say whether disturbances in infant development as indicated by the standard milestones or other abnormalities, for example hearing deficits, which might conceivably be a consequence of an early disturbance of the foetus *in utero*, occur more frequently if amniocentesis is carried out. Indeed it is by no means clear how long such follow-ups should be continued, for example, till the age of 3 years, 5 years, or 10 years? Certainly the problem of organizing such studies, if they are to provide critical answers, is quite formidable.

Because of these uncertainties, and also for the very practical reason that the facilities at present available are extremely limited, particularly for the cell culture side of the procedure, a considerable

degree of selection of those pregnancies to which the procedure is applied, is inevitable. And the basis for this selection is central to the whole matter.

Obviously the object is to identify those pregnancies which have the greatest risk of involving a severely abnormal foetus whose abnormality can be diagnosed with reasonable certainty by available techniques. The grounds on which the selection is based vary considerably from case to case, but the question can be most conveniently considered in terms of four main diagnostic categories:

1. Chromosome abnormalities in which the diagnosis is based on cytogenetic techniques.
2. X-linked disorders in which specific diagnosis is not yet possible, but where the determination of the sex of the foetus is the guide for action.
3. Metabolic disorders, the so-called 'inborn errors of metabolism', in which the diagnosis depends on assay of a specific enzyme or possibly some other biochemical characteristic.
4. Malformations such as anencephaly and spina bifida where the estimation of α-foetoprotein in amniotic fluid is informative.

It is perhaps useful to start with some idea of the relative incidence of cases in these different categories for which amniocentesis has been carried out during the last few years.

Milunsky (1) circulated a questionnaire to all centres in the USA and Canada who undertake amniocentesis for prenatal diagnosis, and his summary of their experiences is given in Table 1. It is based on replies from 41 different centres and probably includes most of the cases in these countries at the time the questionnaires were circulated. Out of the 1,663 pregnancies studied, the findings in 127 (7·6 per cent) indicated that the foetus was abnormal (or in the case of the X-linked disorders had a 50 per cent chance of being abnormal), and of these 102 were aborted. By the time of the survey, 893 apparently normal infants had been delivered.

Of the 1,663 investigations, 1,368 (82 per cent) had been undertaken because of the suspicion of a chromosomal abnormality, 115 (7 per cent) because of an X-linked disorder in the family, and 180 (11 per cent) because of the suspicion of a metabolic disorder.

TABLE 1. *Cumulative US and Canadian experience with amniocentesis for prenatal genetic studies. From Milunsky (1)*

Indications	*Cases studied*	*'Affected' foetuses*	*Selective abortion*	*Prenatal diagnosis confirmed*	*Normal births delivered*
1. Chromosomal disorders					
(*a*) Translocation carriers	93	17	17	17	58
(*b*) Maternal age >40 years	347	9	7	7	190
(*c*) Maternal age 35–39 years	255	4	3	3	122
(*d*) Previous trisomy 21 (mongolism)	485	5	4	3	281
(*e*) Miscellaneous	188	1	1	1	94
2. X-linked disorders	115	54	40	34	39
3. Metabolic disorders	180	37	30	26	109
Total	1,663	127	102	91	893

The experiences of centres in the UK and in Europe were probably very similar during the same time period, though less extensive.

However, it will be noted that the tabulation includes no examples of amniocentesis undertaken to detect anencephaly or spina bifida by α-foetoprotein determination in the amniotic fluid. This is simply a consequence of the fact that the possibility of this test is such a recent discovery, that at the time the questionnaire was carried out it had not yet been applied in practice. It is likely that before long this indication for amniocentesis will begin to rival the chromosomal category in its frequency. This illustrates how rapidly the situation is changing, and the difficulty in predicting future developments on the basis of past experience.

CHROMOSOMAL ABNORMALITIES

A very considerable number of different chromosomal abnormalities have now been recognized and they vary widely in their clinical consequences (2). Some result in spontaneous abortion in early foetal life; others lead to the birth of a severely malformed infant who usually does not survive very long (eg trisomies 13 and 18); others lead to an abnormal infant who may survive into adult life but who is severely mentally retarded (eg mongolism, trisomy 21); and still others although they permit reasonably healthy development may nevertheless result in some degree of intellectual impairment and sterility (eg XXY and XXX). There are also many chromosomal variations which appear to have no obvious clinical effect at all.

In considering the general question of the selection of pregnancies at risk for chromosomal abnormalities, mongolism provides the best example, simply because it is a relatively frequent condition and in fact has been the principal reason for the majority of prenatal diagnoses so far carried out.

Mongolism occurs in about 1 in 600–800 births. It has, however, long been recognized that its incidence depends on the age of the mother at the time of the pregnancy. The higher the maternal age the greater the risk of mongolism. Paternal age is of course correlated with maternal age so that infants from older mothers tend to have older fathers, but paternal age *per se*, except in a few rare cases, is not an important factor. Because of the maternal age effect

TABLE 2. *Estimated age-specific incidence of Down's syndrome, numbers of live births, and estimated numbers of affected infants with percentages, in England and Wales, 1970. From Griffith (3)*

Maternal age (years)	*Incidence per 1,000 live births (estimated)*	*Number of live births*	*Number of affected infants (estimated)*	
All ages	1·67	784,486	1,312	(100·0)*
Under 20	0·9	80,975	73	(5·6)
20–24	1·0	289,209	289	(22·0)
25–29	1·1	238,228	262	(20·0)
30–34	2·0	114,086	228	(17·4)
35–39	5·0	48,323	242	(18·4)
40–44	15·0	12,756	191	(14·6)
45 and over	30·0	909	27	(2·1)

* Figures in parentheses are percentages.

mongols tend to be born towards the end of a family, but the birth position as such is not a significant contributory factor.

Table 2 summarizes the effect of maternal age on mongol births. It is based on estimates of the maternal age-specific incidence and on the actual numbers of live births born to women of different ages in England and Wales in 1970. The risk that an infant born to a mother over 40 years old will be a mongol appears to be about 1 in 60.

It is interesting to note that in the combined US and Canadian data given in Table 1, 347 pregnancies were investigated because the mother was 40 or more years old and 9 'affected' foetuses were identified (1 in 39). Of these 6 were mongols (1 in 58) so the experience in practice bears out very closely the estimated risk derived in a quite different way. Of the other 'affected' foetuses two were trisomy 18, the incidence of which like mongolism is thought to depend on maternal age. The other 'affected' foetus was XXY (Klinefelter syndrome).

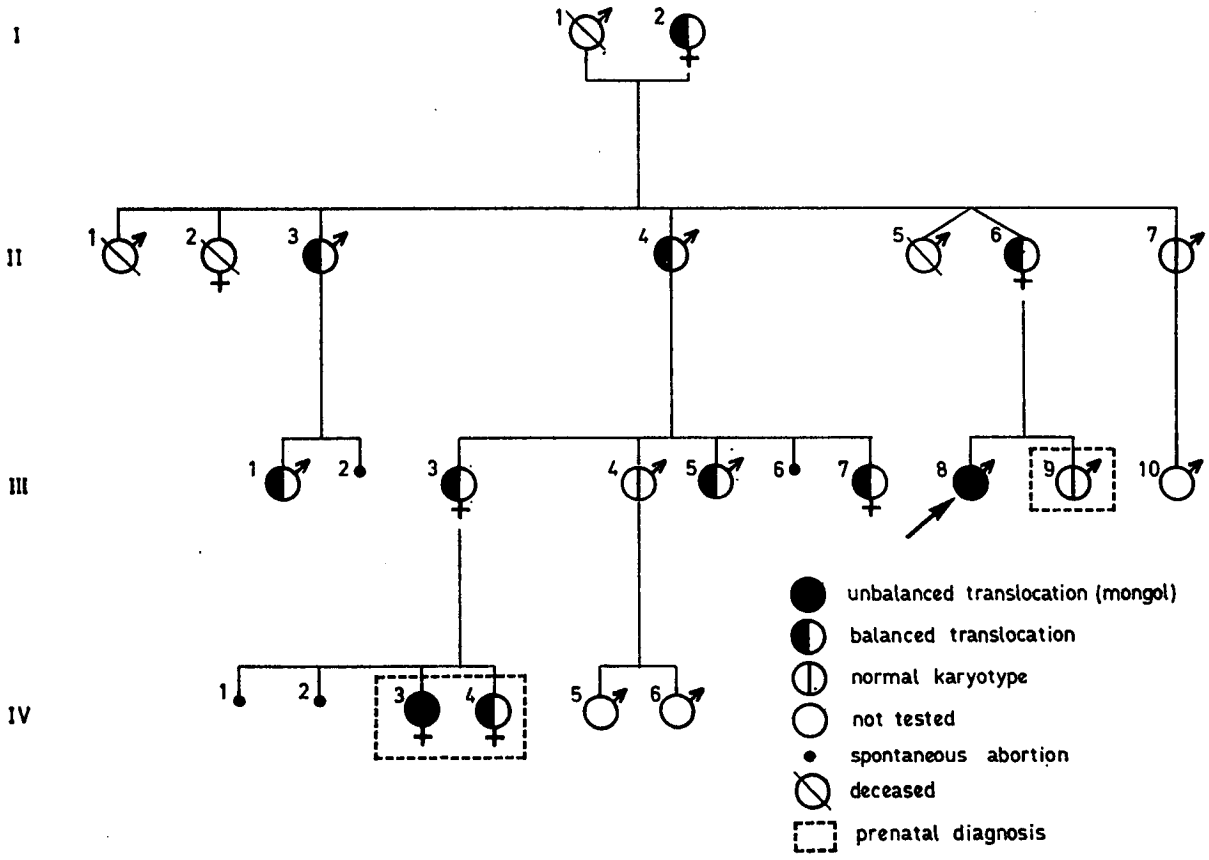
Most mongols have 47 chromosomes instead of the normal 46 (23 pairs). The additional chromosome is no. 21, which is present three times in each somatic cell of the infant instead of twice (hence the name trisomy 21). The abnormality generally arises because in the formation of the ovum in the mother the pair of no. 21 chromosomes fail to separate in meiosis so that the new individual receives

two (instead of one) of these chromosomes from the mother and also one, as is normal, from the father. This phenomenon is known as non-disjunction and evidently is increasingly likely to occur the older the mother.

But in a small proportion (less than 5 per cent) of mongols the chromosomal abnormality is somewhat different, though its clinical effects are essentially the same. In these patients there are 46 chromosomes, including two no. 21s as in the normal, but one of the other chromosomes is abnormal because it has joined to it a large part of a no. 21, so in effect there are three no. 21s. Such an abnormality is known as a translocation and arises as a result of the breakage and aberrant reunion of two different chromosomes, one of which in this case is chromosome no. 21. The translocation may have taken place in the germ cells of one of the parents, so that their chromosomes when examined in somatic cells (eg lymphocytes) are quite normal. But in other cases the 'mutational' event giving rise to the translocation occurred in one of their ancestors. The parent (most frequently the mother) who has actually transmitted the abnormal translocated chromosome to the mongol patient is herself healthy because she has 45 chromosomes including only one ordinary chromosome 21 which she received from one parent and one which is the abnormal chromosome with the translocated no. 21 which was received from the other.

So she has effectively a normal chromosomal complement with two representatives of chromosome no. 21. She (or he) can be said to have a balanced translocation and is a 'translocation carrier'. The mongol patient arises because in the course of meiosis in the parent who is a translocation carrier both the translocated chromosome and the normal no. 21 happen to pass into the gamete which he receives from that parent.

Clearly where a mongol patient is found to represent an example of such an unbalanced translocation, and one or the other of the parents is the carrier of the translocation, then there is quite a significant risk that further children born to the couple will also have unbalanced translocations and therefore mongolism. The risk in fact appears to vary according to which other chromosome the no. 21 is translocated to, and also whether the 'translocation carrier' is the mother or the father, but is perhaps on average


I
II
III
IV
unbalanced translocation (mongol)
balanced translocation
normal karyotype
not tested
spontaneous abortion
deceased
prenatal diagnosis

around 10–20 per cent. However, each reciprocal translocation is a unique event and there is no doubt much variation in the risk. In the extreme situation where there is a translocation which happens to involve two no. 21s, all the liveborn offspring of the 'translocation carrier' will be affected.

Where a mongol patient is found to have an abnormal translocated chromosome involving no. 21 and some other chromosome, and the same abnormal chromosome is found in one of the parents, then chromosome studies (on lymphocytes) from other immediate relatives of that parent are likely to lead to further apparently normal individuals being identified as 'translocation carriers'. Their offspring are similarly at risk. A typical illustration of this sequence of events is illustrated by the family study shown in Fig. 1.

Unbalanced translocations involving chromosomes other than no. 21, also give rise to congenital abnormalities, and in some cases one of the parents is found to be a 'translocation carrier'. Here, as in the equivalent mongol case, there is a quite significant risk attached to future pregnancies in the same couple and to the offspring of other relatives found to be carriers of the same translocation.

FIGURE 1. Pedigree of a family in which an abnormal translocated chromosome (15/21 centric fusion) is segregating.

The propositus (III_8) was a child with mongolism who was found on chromosome analysis to have the abnormal chromosome (15/21) and also two no. 21 chromosomes. His mother (II_6) was found to be a carrier of the abnormal chromosome, but to have only one normal chromosome no. 21. Amniocentesis was carried out during her second pregnancy and the foetus (III_9) was found to be chromosomally normal.

Chromosome studies on various relatives of II_6 led to the discovery that a number of other healthy members of the family were carriers of the abnormal chromosome, as shown in the pedigree. Among these relatives was III_3 who was identified, just before her marriage, as a translocation carrier. Her first two pregnancies (IV_1 and IV_2) ended in spontaneous abortions before 14 weeks. Amniocentesis was carred out in her third pregnancy and the foetus (IV_3) was found to have the abnormal translocated chromosome as well as two no. 21 chromosomes, as in the mongol patient III_8. It was selectively aborted at 18 weeks. Amniocentesis was carried out in the fourth pregnancy and the foetus (IV_4) was found to be a carrier of the abnormal chromosome, with only one no. 21 chromosome, like the mother III_3. The pregnancy was therefore allowed to proceed to term.

These studies were carried out by Dr M. Lucas, Galton Laboratory.

Among the 93 pregnancies of translocation carriers listed in Table 1, 17 affected foetuses (18·3 per cent) were identified.

Quite apart from familial mongolism due to translocation, there is a small but significant familial incidence of mongolism of the ordinary trisomy 21 type. Thus for mothers who have already had one mongol child of this sort there is an increased risk of having another in subsequent pregnancies. This increased risk is probably greater in mothers who have already had a mongol child when relatively young (for example, below 25 or 30 years of age). But on average the risk appears to be about 1 in 100 for all pregnancies in women under the age of 40, who have already had a mongol child. Over the age of 40 the risk is further increased because of the maternal age effect.

The causes of the increased familial incidence of mongolism, other than that due to translocations, are not clearly understood and they probably vary from case to case. In some instances it is believed to be due to the fact that one of the apparently healthy parents (probably usually the mother) is mosaic; some of her cells having a normal chromosomal constitution, but others being trisomic for chromosome no. 21. This condition can occur as a result of an abnormal cell division at some point in the course of the individual's development. At present it is technically rather difficult to identify mosaicism in apparently healthy people on a routine basis, though conceivably this might become easier in the future and might prove a useful guide to assessing the risk of mongol births.

In general then, it is possible using these various criteria to select pregnancies with some increased risk of mongolism. Much the highest risk occurs in the relatively uncommon situation where one of the parents is known to be a carrier of a translocation involving chromosome no. 21. After this come pregnancies in mothers over the age of 40. Then pregnancies in women who have already had a mongol child. Following this are pregnancies in women between the ages of 35 and 39 (risk about 1 in 200).

Where the age of the mother is the criterion for selection, then there is an increased chance of picking up other types of trisomy whose incidence is also influenced by maternal age.

X-LINKED ABNORMALITIES

Chromosomal analysis of amniotic cells grown in tissue culture tells one the sex of the foetus, since females normally have two X-chromosomes and males have one X-chromosome and one Y-chromosome. Consequently in pregnancies where prenatal diagnosis has been carried out because of a suspected chromosomal abnormality and where no such abnormality was found, the mother can be in the unusual position of knowing the sex of her baby at a quite early stage of the pregnancy.

In certain pregnancies, however, where there is believed to be a risk that the foetus will be affected by a disorder determined by an abnormal gene located on the X-chromosome, amniocentesis is carried out for the specific reason of determining the sex of the foetus. The sex can, in fact, often be determined by direct examination of the amniotic fluid cells using certain staining techniques which either detect the so-called sex-chromatin mass or Barr body which is in general characteristic of females, or the Y-chromosome because of its fluorescent characteristics when stained with certain acridine derivatives and which is characteristic of males. But for various technical and other reasons these much quicker methods although accurate in most cases are not 100 per cent reliable and it is usually considered desirable to grow the cells in culture as well, so that a more certain diagnosis of the sex can be obtained by chromosome analysis.

Many quite severe disorders are known to be determined by an abnormal or mutant gene located on the X-chromosome, and to be inherited as so-called X-linked recessive abnormalities. In such cases the disorder is manifested in males whose single X-chromosome has the abnormal gene. But females who carry the gene are, as a rule, heterozygotes and clinically unaffected. The abnormal gene is present on one of their two X-chromosomes, but its normal equivalent or allele is present on the other and this is generally sufficient to prevent overt clinical abnormality of any severity. So characteristically the clinical disorder occurs in males, but is transmitted through females.

In a pregnancy of a female heterozygote by a normal male, there is a 50 per cent chance that a male foetus will have the abnormal

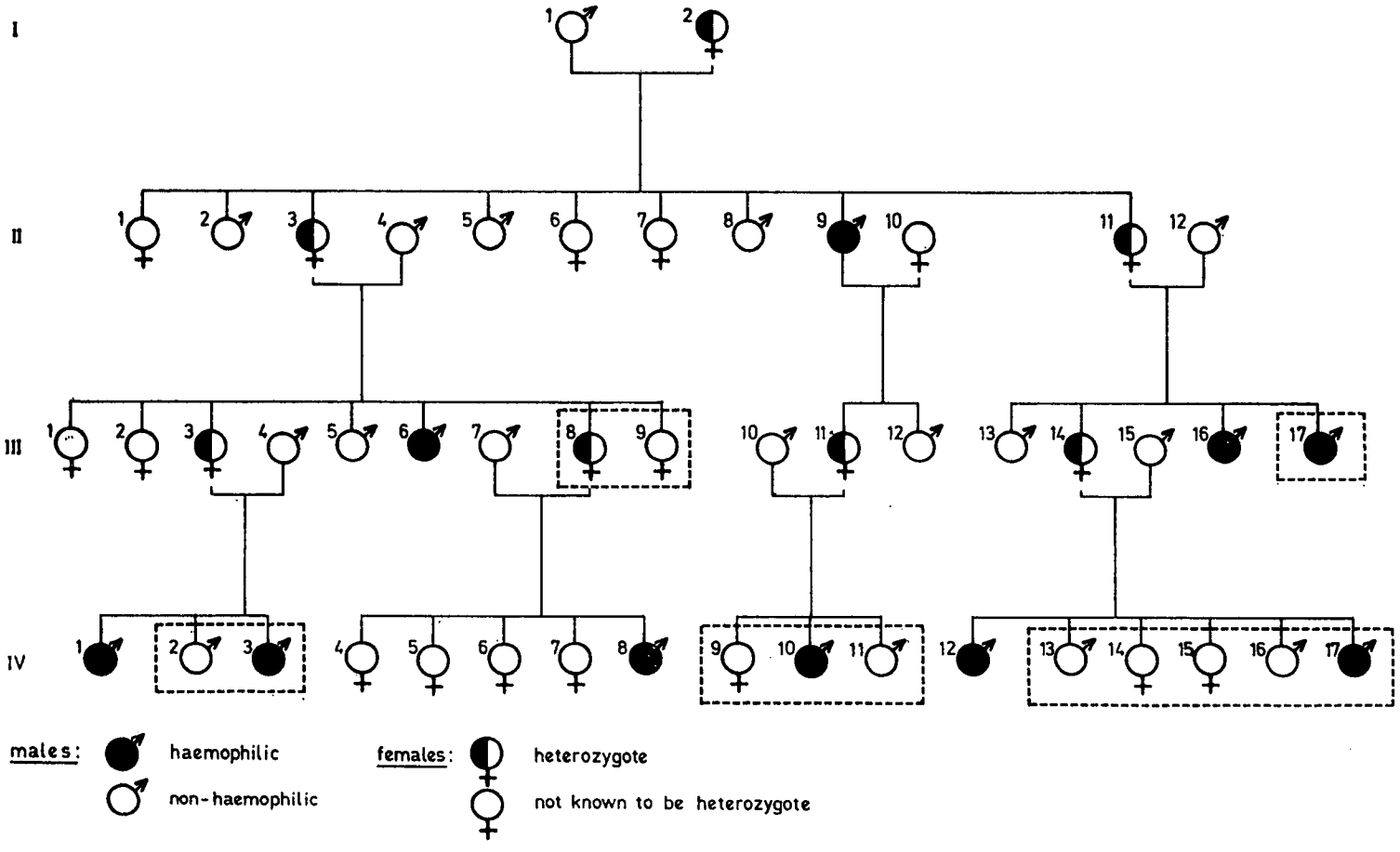

I
II
III
IV
males:
haemophilic
non-haemophilic
females:
heterozygote
not known to be heterozygote

FIGURE 2. Pedigree [after Haldane (4)] illustrating the segregation of the gene for haemophilia among the descendants of Queen Victoria (I_2). Only those branches of the family in which haemophilic patients are known to have occurred are shown.

Queen Victoria must have been heterozygous for the haemophilia gene because one of her sons, Leopold (II_9) suffered from haemophilia, and because haemophilia occurred among the children and grandchildren of two of her daughters, Alice (II_3) and Beatrice (II_{11}).

Queen Victoria's grand-daughter, Alice (III_{11}), must have been heterozygous for the haemophilia gene, since she was the daughter of a haemophilic patient (Leopold, II_9). If what is known today had been known then, and if amniocentesis and the selective abortion of the male offspring of female carriers of the haemophilia gene had been considered acceptable (which is hardly likely), then the three pregnancies IV_9, IV_{10}, and IV_{11} might have been subject to amniocentesis with the selective abortion of the foetuses identified as male (IV_{10} and IV_{11}).

With present knowledge, but in the absence of a direct test for detecting heterozygotes, Queen Victoria's daughter, Alice (II_3), would only have been recognized as a heterozygous carrier after the birth of her haemophilic son, Frederick (III_6). Thus only her two last pregnancies (III_8 and III_9) could have been considered candidates for amniocentesis. Similarly, Irene (III_3) would only have been identified as a heterozygous carrier after the birth of her haemophilic son, Waldemar (IV_1); Alexandra (III_8), Tsarina of Russia, would only have been identified as a heterozygous carrier after the birth of her last child, Tsarevitch Alexis (IV_8) who was haemophilic; Victoria Eugenie (III_{14}), Queen of Spain, would only have been recognized as a heterozygous carrier after the birth of her first son, Alfonso (IV_{12}).

The pregnancies which might have been candidates for amniocentesis and selective abortion if the procedure had been known about and considered acceptable are indicated in the pedigree by

Selective abortion might have led to the elimination of eight male foetuses, four of which were subsequently known to have been haemophilic.

Key to individuals shown in the pedigree

I: I_1: Prince Albert of Saxe-Coburg-Gotha.
I_2: Victoria, Queen of England.

II: II_1: Victoria (married Frederick III, Emperor of Germany); II_2: Edward VII, King of England; II_3: Alice; II_4: Ludwig, Grand Duke of Hesse; II_5: Alfred, Duke of Edinburgh; II_6: Helena (married Prince Christian of

(continued overleaf)

gene and therefore be affected and a 50 per cent chance that it will be normal. If the foetus is female, a normal child may be expected though there is a 50 per cent chance that it will be heterozygous like the mother. In a pregnancy where the father is affected but the mother is normal, it can be expected that a child of either sex will be unaffected clinically, though all the daughters will be heterozygotes.

Thus where the mother is known to be heterozygous for an abnormal X-linked gene which results in a severe disorder, prenatal diagnosis of the sex of the foetus may be undertaken if it is desired to prevent the birth of an affected child. Abortion of a male foetus but not of a female foetus will ensure that infants with the particular abnormality will not be born. But such a procedure, of course, involves aborting normal male foetuses in about one-quarter of the cases, since on average half the foetuses found to be male are expected to be normal.

The general point is illustrated by the pedigree shown in Fig. 2. This shows the occurrence of the X-linked disorder, haemophilia,

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FIGURE 2, *continued)*

Schleswig-Holstein); II_7: Louise (married Duke of Argyll); II_8: Arthur, Duke of Connaught; II_9: Leopold, Duke of Albany, died age 31 from haemorrhage after a fall; II_{10}: Helena of Waldeck; II_{11}: Beatrice; II_{12}: Henry, Prince of Battenburg.

III: III_1: Victoria (married Prince Louis Alexander of Battenburg, III_{13}); III_2: Elizabeth (married Grand Duke Sergius of Russia); III_3: Irene; III_4: Henry, Prince of Prussia (son of Victoria, II_1, and Frederick III, Emperor of Germany); III_5: Ernest, Grand Duke of Hesse; III_6: Frederick (died age 3 of haemorrhage after a fall); III_7: Nicholas II, Tsar of Russia; III_8: Alexandra; III_9: Mary; III_{10}: Earl of Athlone; III_{11}; Alice; III_{12}: Charles Edward, Duke of Albany; III_{13}: Louis Alexander, Prince of Battenburg; III_{14}: Victoria Eugenie; III_{15}: Alfonso XIII, King of Spain; III_{16}: Leopold, Lord Mountbatten, died age 33; III_{17}: Maurice, Prince of Battenburg, died age 23 (casualty in First World War).

IV: IV_1: Waldemar, Prince of Prussia; IV_2: Sigismund; IV_3: Heinrich (died age 4); IV_4: Olga; IV_5: Tatania; IV_6: Marie; IV_7: Anastasia; IV_8: Alexis, Tsarevitch of Russia; IV_9: May (married Captain Henry Abel Smith); IV_{10}: Rupert, Lord Trematon (died age 21 following car accident); IV_{11}: Maurice (died in infancy); IV_{12}: Alfonso, Duke of Asturias (died age 31 after car accident); IV_{13}: Jaime; IV_{14}: Beatrice; IV_{15}: Maria; IV_{16} Juan; IV_{17}: Gonzalo (died age 20 after car accident).

in certain members of the Royal houses and nobility of Europe who were descendants of Queen Victoria (I_2). It turns out that Queen Victoria herself must have been heterozygous for the abnormal gene which determined this particular form of haemophilia, which was quite severe. If present-day knowledge had been then available, her grand-daughter (Princess Alice, III_{11}) would have been identified as being heterozygous since she was the daughter of Queen Victoria's son (Leopold, II_9) who was haemophilic. If prenatal sex determination had been possible and abortion of male foetuses regarded as acceptable, which is unlikely, then each of her pregnancies (IV_{9-11}) would perhaps have been monitored, and her sons aborted. Certain other female heterozygotes in the family (for example, Queen Victoria's daughters: Princess Alice, II_3, and Princess Beatrice, II_{11}; and her grand-daughters: Victoria Eugenie, Queen of Spain, III_{14}; Alexandra, Tsarina of Russia, III_8; and Princess Irene of Prussia, III_3) would only have been certainly identifiable as heterozygotes after they had already borne a haemophilic son. In these cases subsequent pregnancies might have been regarded as appropriate for the procedure. It would have meant the early elimination of some of their haemophilic sons, but also of some non-haemophilic sons.

Not all males with an X-linked abnormality are the offspring of a heterozygous mother who has received the abnormal gene from one of her ancestors. A proportion of cases will be the consequence of the occurrence of a fresh mutation in the germ cells of the mother. In these circumstances there will usually be no significant risk of the occurrence of the abnormality in her subsequent pregnancies. Fresh mutations of this sort may account for up to one-third of the cases of severe X-linked disorders which either lead to death before the age of reproduction or for some other reason render him infertile. Thus the birth of an affected male does not necessarily mean that the mother is heterozygous and that future pregnancies are 'at risk' though this is generally so in at least two-thirds of the cases. Once an affected son has been born, the mother can be regarded as heterozygous if there is a family history of the disease of the sort shown in the pedigree in Fig. 2, such that, for example, a brother or a maternal uncle of the mother is known to have had the disorder. However, the family history may not be

very informative because the members of the family have lost touch, or the medical records are poor, or for some other reason.

In these circumstances a direct test which would enable one to tell whether the mother is in fact heterozygous would clearly be valuable. A test thought to be capable of detecting a high proportion of the heterozygotes in haemophilic families has been described (5). But it is technically rather specialized and not generally available. A test for heterozygosity is, however, often used in the case of the X-linked Duchenne type of muscular dystrophy. Here it has been shown that in known heterozygotes the level of activity of the enzyme creatine kinase measured in serum is on average significantly higher than in appropriate control subjects (6). Although the test, even when carried out under optimal conditions and with replications, does not permit certain discrimination of heterozygous from non-heterozygous women in families where Duchenne muscular dystrophy is known to occur, it does appear to be capable of picking out some 70–80 per cent of the heterozygous carriers in such 'at risk' families (Appendix 2).

The detection of heterozygous carriers in some such way as this is likely, of course, to be particularly useful in cases where a woman has not yet had an affected child but is known to be a possible heterozygote because of an affected brother or maternal uncle. In such circumstances if she is found by the test to have a higher probability of being heterozygous, she then has the potential option of either foregoing further pregnancies or having them monitored with the consequent abortion of male foetuses but the possibility of having healthy daughters.

In a small number of X-linked disorders such as Fabry's disease, the Lesch-Nyhan syndrome and Hunter's syndrome, it is possible to make a direct diagnosis of the abnormality by enzyme or metabolic studies on amniotic fluid cells grown in tissue culture. Obviously if abortion is intended, this is preferable to basing the decision simply on the sex of the foetus, since the possibility of aborting a normal foetus is thereby avoided.

METABOLIC DISEASES

A considerable number of different inherited metabolic diseases, so-called inborn errors of metabolism, have now been identified, though most of them are very rare. The characteristic metabolic and clinical abnormalities which occur in these conditions, can in general be attributed in each case to a gross deficiency of a specific enzyme (7). They are usually determined by abnormal genes located on one or other of the 22 pairs of autosomal chromosomes, though a few have been shown to be due to genes located on the X-chromosome.

As a rule the conditions are 'recessively' inherited. That is to say in the case of the autosomal conditions, the affected individuals with the severe enzyme deficiency have two abnormal genes (alleles), one derived from one parent and one from the other. The parents themselves are generally heterozygotes, and at the particular chromosomal locus concerned the abnormal gene is present on one of the pair of homologous chromosomes, while its normal counterpart or allele is present on the other. Such heterozygous individuals are usually quite healthy, because the single normal allele present is able to determine the synthesis of a sufficient amount of the particular enzyme to allow the metabolic process with which it is concerned to proceed in an essentially normal manner. However, the level of activity of the enzyme in the tissues of such heterozygotes is often on average reduced to about half the level present in individuals homozygous for the normal allele, because there is only one normal allele acting instead of two.

In a pregnancy derived from a mating between two such heterozygous individuals, the chance that the foetus will have received the abnormal gene from each parent and so have a severe deficiency of the enzyme is 1 in 4. The chance that the foetus is heterozygous like the parents is 1 in 2 and the chance that it is a normal homozygote is 1 in 4. So once a child affected with one of these autosomal recessive metabolic disorders has been born to a particular couple, the risk of the same disorder occurring in a subsequent pregnancy is 1 in 4. In practice the question of prenatal diagnosis only arises in the great majority of these conditions, after an affected child has already been born and subsequent pregnancies have thus been identified as being 'at risk'.

The possibility of prenatal diagnosis in such cases depends, in general, on the demonstration of the gross deficiency of the specific enzyme characteristic of the disease in amniotic fluid cells grown in tissue culture, and on the ability to distinguish this marked enzyme deficiency from the partial enzyme deficiencies usually present in heterozygous foetuses who can of course be expected to develop into healthy infants. This in turn is contingent on whether or not the enzyme actually occurs in tissue-cultured amniotic cells from a normal homozygous foetus.

A good guide as to whether a particular enzyme will be present in cultured amniotic fluid cells from a normal foetus is provided by studies on fibroblasts grown in tissue culture and derived from a skin biopsy obtained in childhood or adult life. In the last few years such fibroblast cultures have been examined for a considerable variety of enzymes and many of these have been shown to occur in sufficient quantity to allow a reasonably reliable assay. Furthermore, where such studies have been carried out on fibroblasts derived from skin of patients suffering from a variety of different inherited metabolic diseases and from their heterozygous relatives, the marked enzyme deficiency characteristic of the disease and the partial deficiency occurring in heterozygotes has generally been clearly demonstrable. Also, good discrimination has usually been obtained between the levels of enzyme activity observed in the heterozygotes and those found in the clinically affected patients. As a general rule it appears that the same is true for these enzymes when assayed in cultured amniotic cells.

However, it is important to note that some enzymes are not detectable in fibroblast cultures, and if a deficiency of such an enzyme is the basis of a particular inherited metabolic disorder, then prenatal diagnosis by this approach is not feasible. Phenylketonuria is an example. The enzyme phenylalanine hydroxylase, the deficiency of which in the liver in this condition is the cause of the metabolic disorder, is not detectable in cultured fibroblasts from normal individuals. Consequently prenatal diagnosis is not as yet possible.

A list of some of the inborn errors of metabolism in which it has been shown that a reliable prenatal diagnosis can be made by enzyme assay or related biochemical studies on amniotic fluid

cells grown in culture is given in Appendix 3. Most of these conditions are extremely rare, and the particular enzyme assays or other biochemical studies required, tend to be quite specialized and sophisticated and outside the routine ambit of most laboratories. An important difference from the prenatal diagnosis of chromosomal abnormalities is that whereas essentially the same techniques of chromosome analysis are applicable to the detection of all chromosomal abnormalities even though the abnormalities may vary widely in their detailed nature from one to another, most of the metabolic disorders require a special methodology for each condition.

The rarity of any particular disorder and the specialized nature of the techniques required for its prenatal diagnosis, obviously poses problems in making arrangements for the appropriate investigations to be carried out, when a pregnancy 'at risk' happens to be identified. A further difficulty is that although it may be possible to discriminate between the enzyme levels occurring in affected foetuses and those in heterozygous foetuses, under particular standardized tissue culture conditions and enzyme assay procedures, it is known that the actual enzyme activities which occur are likely to vary, sometimes quite widely, with the actual conditions of tissue culture and the details of the assay method adopted. Consequently the findings are likely to be unreliable if the enzyme assay values obtained are assessed simply in relation to normal values reported in the literature or even those obtained previously in the same laboratory. In practice it is necessary to have available for simultaneous assay an adequate number of control cultures derived from amniotic fluid cells and grown under the same culture conditions. Clearly, centralized laboratories capable of undertaking a range of enzyme assays and with an adequate supply of control material are likely to be necessary if this type of prenatal diagnosis is going to be undertaken on any extensive basis. At present most of the work of this sort is being done in a few laboratories each of which has specialized in particular conditions or sets of related conditions. These *ad hoc* specialized centres have usually arisen because of the specialized research interests of the particular laboratories.

Detecting heterozygotes

An obvious limitation of the prenatal diagnosis of rare metabolic diseases inherited as autosomal recessives, is that the pregnancies 'at risk' are usually only identified because of the previous birth of an affected infant. When this has occurred it indicates that both the parents, though quite healthy, are both heterozygous for the particular abnormal gene involved. Obviously if such heterozygous couples could be identified in advance, then all their pregnancies could be monitored. In practice, however, this possible approach is beset with very formidable difficulties for the great majority of such conditions.

It is known that, as a rule, heterozygotes for genes determining these disorders have reduced activity levels of the specific enzyme, usually amounting to about half the activity found in normal heterozygotes (7). This has been established by comparing the average activity of the specific enzymes in healthy parents of patients with the particular disorder, with a random series of control subjects. The parents represent a series of heterozygotes and the random control subjects are effectively a series of normal homozygotes, since heterozygotes occur only infrequently in the general population. The enzyme activities for such studies have usually been carried out on reasonably accessible material such as red cells, white cells, serum, or fibroblasts grown in culture, according to the normal tissue distribution of the particular enzyme. While a significant difference between the mean values for the heterozygotes and the control subjects has been demonstrated over an extensive range of conditions, it has, however, usually been found that there is considerable variation from person to person within each group. And as a rule the two distributions of values overlap. Thus it is often not possible to discriminate from the assay values, between individuals in the lower ranges of the control distribution and individuals in the upper ranges of the heterozygote distribution. The amount of overlap varies from enzyme to enzyme, but it is uncommon to find a situation where, even if the control and heterozygous samples are roughly equal in number, less than a few per cent of each sample falls into the range of the other. This degree of discrimination may be adequate to pick out individuals with a reasonably high

probability of being heterozygotes in a study confined to the immediate relatives (for example, uncles, aunts, cousins, and grandparents) of an affected patient, because a quite high proportion of such relatives are likely to be heterozygous. But if a large random population of individuals is screened with the aim of identifying such heterozygotes, the accuracy of their detection is very much less. This is simply because the incidence of heterozygotes for a gene determining a particular rare metabolic disorder is usually less than 1 in 200–400 of the population studied. Consequently it is difficult to identify the heterozygotes from many normal individuals whose enzyme levels happen for some other reason to place them in the tail of the distribution.

The causes of variation in enzyme activity both among individuals thought to be homozygous for the normal allele, and among individuals heterozygous for the allele which in homozygotes results in the particular clinical disorder, are still in most cases quite obscure. In part, the observed variation may arise from the methods used in the enzyme assay, and if so technical improvements in the future can be expected to improve the discrimination of heterozygotes in population surveys. But the variation may also in part result from genetic heterogeneity. Other alleles, for example, may affect the activity of the enzyme without necessarily resulting in overt clinical abnormality even in the homozygous state.

A relatively simple illustration is provided by studies of the enzyme whose deficiency gives rise to the metabolic disorder, galactosaemia. Patients with this disorder, which is inherited as an autosomal recessive, show a complete or virtually complete absence of the enzyme galactose-1-phosphate uridyl transferase. Their parents who may be presumed to be heterozygous for the abnormal allele show on average about 50 per cent of normal enzyme activity. However, quite unexpectedly in the course of an investigation in the general population by routine enzyme assay in red cells from a large number of randomly selected healthy individuals, another much more common allele causing a reduction in activity of this enzyme was discovered (8). Individuals homozygous for this other allele (usually referred to as the Duarte variant) have on average about the same levels of activity as heterozygotes for the allele determining galactosaemia. Heterozygotes for this

allele and the so-called 'normal allele', have levels of activity intermediate between the average levels of the normal homozygotes and the homozygotes for the Duarte variant (Appendix 4).

Like the heterozygotes for the galactosaemia causing allele, these homozygotes for the new allele are quite healthy. The two genotypes can be discriminated by more complex enzyme studies and by additional family studies, but the detection of heterozygotes for galactosaemia by routine assay of the enzyme in population surveys is a more complex business than might have been anticipated at first sight (8). Such complexities are, of course, superimposed on the complexities due to other causes of variation in enzyme level within each of the different genotypes.

Similar complexities are likely to be found as other enzymes, the deficiencies of which cause specific metabolic diseases, are studied in population surveys, and it is by no means clear at present to what extent these causes of enzyme variation will complicate proposed population screening programmes for the detection of heterozygotes.

Thus, in general, the screening of populations in order to identify couples who have a 'high risk' (1 in 4) of having an affected child, prior to the birth of one such affected infant, is not a practical approach at the present time for the great majority of the autosomal recessive inborn errors of metabolism where prenatal diagnosis is feasible. Even assuming that methods are eventually found for identifying heterozygous parents at risk with greater certainty, the practical difficulties imposed by the fact that there are a considerable number of rare recessive disorders, each involving an abnormality of a different enzyme, and that the detection of heterozygotes will involve a special technical procedure for each enzyme, will clearly present considerable problems.

Probably the only conditions in which this general approach of identifying pregnancies at risk by population screening for heterozygotes can at present be considered seriously, are those where the particular disorder happens to have a relatively high incidence in a particular population and where the technical methods available for the detection of heterozygotes in random population surveys are unusually good. Of course it is also necessary that a satisfactory method for prenatal diagnosis has been established.

Perhaps the only severe disorder in which these requirements can be regarded as having been met at the present time is Tay-Sachs's disease in communities of Ashkenazi Jews (9). However, it seems not unlikely that within a few years other conditions such as fibrocystic disease, sickle cell anaemia, and β-thalassaemia, may also come within the same category (see pp. 38–43). And each of these conditions represents numerically a very much larger problem than Tay-Sachs's disease. So the pilot studies which have been carried out in Ashkenazi Jews in order to identify pregnancies 'at risk' by population screening for heterozygotes for Tay-Sachs's disease, are of general interest in that they provide background information against which future proposals involving more widespread disorders can be evaluated.

Tay-Sachs's disease, which is inherited as an autosomal recessive, is a severe progressive neurological disorder usually fatal in early childhood. It is unusually common in communities of Ashkenazi Jews, where about 1 in 2,500 newborn may be affected. In other populations the disorder in its various forms is probably about one hundred times less frequent than this. It has been shown that the metabolic and clinical abnormality in the form of Tay-Sachs's disease which is common in Ashkenazi Jews, is the consequence of a complete or virtually complete deficiency of the enzyme N-acetylhexosaminidase A. This enzyme deficiency can be demonstrated in tissue-cultured amniotic fluid cells so that prenatal diagnosis is feasible. Indeed prenatal diagnosis, with the abortion of affected foetuses, is already quite extensively practised in pregnancies where the foetus was known to be at risk because of the previous birth of an infant with Tay-Sachs's disease.

Studies of the enzyme in serum and also leucocytes of parents of patients with Tay-Sachs's disease led to the development of a procedure for distinguishing heterozygotes for the Tay-Sachs's gene from other individuals. This procedure (9) while not giving complete discrimination is said to provide an accurate result in some 95 per cent of cases under routine survey conditions, and additional studies on those individuals where the original test is indecisive can be carried out to improve the discrimination further (> 99 per cent). This unusually good degree of heterozygote detection, combined with the high incidence of the disorder among Ashkenazi

Jews among whom some 4 per cent of randomly chosen individuals might be expected to be heterozygous, made a pilot study of the feasibility of identifying pregnancies 'at risk' a viable proposition.

The first and so far most extensive study of this sort was carried out by Kaback and his colleagues on the Ashkenazi Jewish community living in Baltimore, Maryland, USA (9). It was initiated in 1971, after rather more than a year's intensive work in the community explaining the aims of the study and combining this with a broad educational programme in order to convey the essential genetic principles on which it was based, and directed at achieving general support and backing from the religious and other community leaders as well as from the members of the community as a whole. In addition satisfactory procedures had to be developed for coping with large numbers of blood samples, and assaying them accurately.

In the first two years of the project approximately 10,000 individuals volunteered to be tested and 1 in 24 (0·042) were identified as heterozygotes. Eleven couples, none having previously had a child with Tay-Sachs's disease, were identified as both being heterozygous. At the time of the last report five of these couples had conceived, and all had elected to have the pregnancy monitored by amniocentesis and in one instance the prenatal diagnosis indicated Tay-Sachs. This foetus was aborted and post-mortem studies on the abortus confirmed the diagnosis.

This study certainly demonstrates the feasibility of this approach in the case of Tay-Sachs's disease. But it also illustrates the considerable deployment of resources needed to mount and sustain such a programme, even under the relatively favourable conditions provided by the general social and cultural circumstances evidently existing in the Baltimore Jewish community. In other less tightly knit Jewish communities the problem of achieving such a response would presumably be much more difficult. Also the project raises questions about the psychological and social consequences of a sustained campaign focusing attention on a single abnormality peculiar to one section of a population.

ALPHA-FOETOPROTEIN AND NEURAL TUBE MALFORMATIONS

Anencephaly and spina bifida cystica arise from developmental defects in the neural tube, and represent one of the commonest groups of severe congenital abnormality. In the British Isles their combined incidence at birth is about 4–5 per 1,000, though there are marked regional variations. The precise causes of these malformations are not understood, though it appears that both environmental and genetical factors are involved. After the birth of one child in a family with either anencephaly or spina bifida, the risk that a further child will be affected with one or other form of these malformations is about 1 in 20, and after the birth of two such children the risk for further sibs appears to be increased to about 1 in 10 (10). Anencephalic infants are stillborn or die within a day or two. Spina bifida is more variable in its manifestations but often results in severe disability.

Retrospective studies of amniotic fluids obtained from pregnancies with these particular foetal malformations led to the discovery of unusually high concentrations of α-foetoprotein, and this suggested that assay of this substance in amniotic fluid could provide a practical method for prenatal diagnosis (11). Subsequent work has substantially confirmed this expectation, though it is still somewhat unclear as to what proportion of cases, particularly of spina bifida, will be detectable by this approach. Probably only the cases with so-called 'open' lesions will be picked up consistently, but these represent a high proportion of the cases giving severe disability.

Alpha-foetoprotein is a protein which in normal individuals appears to be peculiar to the foetus. It is produced in foetal liver as early as the sixth week of gestation. In foetal serum it reaches its highest concentration at about 13 weeks of gestation and then falls steadily to term. The protein is also detectable in amniotic fluid throughout pregnancy and as in foetal serum the highest levels are found at about 13 weeks. However, the concentration gradient of α-foetoprotein between normal foetal serum and amniotic fluid is about 200:1. It does not seem likely that the synthesis of α-foetoprotein is abnormal in anencephaly or spina bifida, or that the protein is causally related to the development abnormality. Its increased concentration in the amniotic fluid is thought to be due

simply to the fact that the neural tube damage allows proteins from foetal serum to pass more readily into the amniotic fluid.

The first reports (12) are now appearing of 'high risk' pregnancies, selected because of the previous birth of an infant with anencephaly or spina bifida, in which α-foetoprotein was estimated in amniotic fluids obtained at around 16–18 weeks' gestation. Where abnormally high levels of α-foetoprotein were detected, the foetus was aborted and so far a gross neural tube malformation was present in each case (Appendix 5). Although the number of such 'high risk' pregnancies studied in this way is still quite small, the proportion of neural tube malformations identified is consistent with the expectation derived from earlier epidemiological studies. At the time of the reports not all the other pregnancies had come to term, so it remains uncertain how many cases of neural tube malformations were missed. One reported example of a diagnosis missed by α-foetoprotein determination at the sixteenth week of gestation was a case with an apparently 'closed' lesion in which there was a severe encephalocoele and associated skull defect covered by attenuated but complete full thickness skin (13). It was estimated from previous epidemiological and clinical studies that such 'closed' lesions may occur in perhaps 10 per cent of disabling neural-tube malformations which are compatible with survival.

'High risk' pregnancies so defined because of the previous birth of an infant with anencephaly or spina bifida inevitably represent only a small proportion (approximately 10 per cent) of all pregnancies in which such an abnormality may be present. So other ways of identifying pregnancies which are at risk are clearly desirable.

One approach which is currently being investigated involves the determination of the amount of α-foetoprotein in maternal serum in early pregnancy. Normal maternal serum has been shown to contain small but detectable amounts of α-foetoprotein which is presumed to come from the foetus, and there is an increasing body of evidence which indicates that the amount of the protein is somewhat increased in many cases where the foetus has anencephaly or spina bifida (14). The concentration of α-foetoprotein in maternal serum appears to be about 500 times lower than that in amniotic fluid, so much more sensitive and sophisticated methods are required for its determination.

Thus routine determination of α-foetoprotein in early pregnancy might prove useful in picking out pregnancies in which further investigation by amniocentesis would be worth while. The data so far available on the range of variation of α-foetoprotein in maternal serum at the appropriate period in normal pregnancies is still very limited, as is data on maternal serum in pregnancies known to involve foetuses with anencephaly or spina bifida. So the discriminative power of this approach is still uncertain. What data there is, suggests that assays of α-foetoprotein in maternal serum are unlikely to be as effective as direct assays on amniotic fluid in picking out pregnancies with neural tube malformations, and a higher proportion, particularly of spina bifida cases, are likely to be missed. But since such assays on maternal serum could in principle be carried out relatively easily in all pregnancies, this approach may provide a useful way of directing attention to at least some 'high risk' pregnancies in which amniocentesis could then be carried out.

The possibility of obtaining a prenatal diagnosis of 'open' neural tube defects by the detection in amniotic fluid of proteins normally found only in cerebrospinal fluid has also been raised. Preliminary retrospective studies based on the detection of such a protein (referred to as β-trace protein or BTP) have been reported (15). The results are sufficiently hopeful as to indicate that this procedure may prove useful either in addition to, or perhaps instead of, α-foetoprotein determination in amniotic fluid.

A quite different approach to the prenatal identification of neural tube malformations is provided by the technique of 'sonography' using ultrasound. This does not involve direct invasion of the uterus and appears to be quite safe. Indeed it is recommended as a standard procedure for locating the position of the placenta prior to amniocentesis. The technique is also capable of outlining the shape of the foetus, particularly the head, and has been shown to be capable of identifying foetuses with anencephaly. It is not, at least at present, sufficiently sensitive to detect spina bifidas. So it is likely to be used more as an adjunct rather than an alternative to amniocentesis and α-foetoprotein assay, for the prenatal diagnosis of this class of abnormalities.

MULTIPLE TESTS ON AMNIOTIC FLUID SPECIMENS

Although amniocentesis for prenatal diagnosis is in general carried out with a particular diagnosis in mind, the question obviously arises as to how far the amniotic fluid sample once obtained may be used to identify or exclude other major foetal abnormalities.

Where the diagnosis of some particular chromosomal abnormality is the principal reason for carrying out the investigation, then it follows from the nature of the technique of chromosome analysis, that any other kind of chromosomal abnormality present will be detected even if the particular condition for which the investigation was originally undertaken is not itself present. Occasionally therefore unexpected chromosomal abnormalities of sufficient severity to be regarded as justifying abortion will be picked up.

Alpha-foetoprotein assay in order to detect neural tube abnormalities which would of course not be identified by chromosome analysis can also be carried out on the amniotic fluid specimens, if the appropriate assay procedures are available. And it seems likely that this will become a routine procedure whenever amniotic fluid is obtained for other reasons.

However, amniotic fluid cultured cells obtained for chromosomal diagnosis can hardly, at present, be utilized for the routine exclusion of rare metabolic diseases by enzyme assay. This is simply because much larger quantities of cells would need to be grown in culture, and this would impose too great a burden on available facilities; and also because too many different types of enzyme assay would need to be applied to such cells if an attempt were being made to exclude any significant number of the diagnoses of rare metabolic disease which are already possible.

In contrast, where the amniotic fluid sample has been obtained in order to identify or exclude the presence of a particular rare metabolic disorder, the risk of which in that pregnancy is known to be high, chromosomal analysis of the cultured cells and also assay of α-foetoprotein in the amniotic fluid in addition, would be a reasonable practical possibility. And no doubt such studies will in due course become a routine part of this type of investigation.

It also seems reasonable to expect that where amniotic fluid has been obtained for α-foetoprotein determination because the preg-

nancy is thought to be at 'high risk' for a neural tube defect, then routine cell culture and chromosome analysis will become part of the procedure so that gross chromosomal abnormalities, at least, can also be excluded in situations where the α-foetoprotein determinations do not point to the presence of a neural tube abnormality.

FURTHER DEVELOPMENTS

The current spate of research activity in this area leaves one with little doubt that the scope and practice of prenatal diagnosis will expand considerably in the next few years. At present the most highly developed branch of the subject is that concerned with chromosomal abnormalities and perhaps it is in relation to the prenatal diagnosis of metabolic and other non-chromosomal abnormalities where the main thrust of new developments can be expected.

The elucidation of specific enzyme or protein abnormalities in a great variety of at present obscure genetically determined diseases can be expected to occur, and the experience so far suggests that many of these are likely to be detectable in amniotic fluid cells grown in culture and so make the conditions amenable to prenatal diagnosis. Direct studies on the composition of amniotic fluids, or perhaps maternal serum, as in the case of α-foetoprotein and the neural tube defects, may open the way to the prenatal detection of an even wider range of congenital abnormalities. Also technical improvements such as the development of more sensitive and accurate assays for various enzymes or other components of diagnostic significance in tissue-cultured cells, or amniotic fluids, may be expected to simplify and remove some of the difficulties and hazards in the presently available techniques.

There is probably little point in attempting to predict, or rather guess, the changes in the over-all shape of the subject which will result from such discoveries and technical developments. However, it is perhaps worth drawing attention to certain inherited diseases in which it seems likely from current research that reliable methods of prenatal diagnosis will become available fairly soon, and which happen to be particularly important because of their high incidence in certain populations and the considerable morbidity which they

produce. One of these conditions is cystic fibrosis. Others belong to the group of haemoglobinopathies, notably sickle cell anaemia and the various forms of thalassaemia. If prenatal diagnosis is to become generally available for these disorders the organization of the necessary services will inevitably pose considerable problems.

The potential application to prenatal diagnosis of advances in knowledge about genetic linkage also needs mention.

Cystic fibrosis

In populations of European origin cystic fibrosis is the most commonly occurring severe autosomal recessive disease. It appears that about 1 in 2,500 children are affected, which implies that approximately 1 in 25 individuals in the population is a heterozygous carrier of the gene involved. In other ethnic groups, for example Blacks and Orientals, the incidence of the disease appears to be much less (16).

The condition is an important cause of morbidity in childhood and adolescence, and despite recent improvements in the symptomatic treatment of the condition a substantial proportion of affected patients die before reaching adult life. Characteristically there is progressive damage to the lung and defective pancreatic function, due to the blocking of small ducts by excess mucus. Excessive concentrations of salt in sweat and saliva are another typical feature of this disorder.

The basic biochemical abnormality causing the various characteristic pathological features of the condition has not yet been identified. But recent work strongly suggests that whatever this may be, it does in fact occur in fibroblasts grown in tissue culture and that prenatal diagnosis of the condition should be possible once a satisfactory test for the abnormality has been worked out.

One set of findings which lead to this conclusion stem from earlier work which demonstrated that there is in serum from cystic fibrosis patients and also in serum from healthy heterozygotes, a substance, probably a protein, which has the unusual property of disrupting the normal activity of cilia in preparations of mucosa from the trachea of rabbits, and also from the gills of oysters (17). The requirements of these biological assay systems for the so-called

cystic fibrosis ciliary dyskinesia or inhibiting factor are technically difficult, but the results are now sufficiently extensive as to indicate that the presence of this factor in serum provides a good discriminant between normal individuals on the one hand, and cystic fibrosis patients or heterozygous carriers of the cystic fibrosis gene on the other. Furthermore, the presence of the factor has been demonstrated in cell-free media in which fibroblasts from patients with cystic fibrosis and also from known heterozygotes had been grown, but was evidently not present in media from the great majority of the controls. Because of the high incidence of heterozygotes in the general population, occasional positive results in normal control samples are of course to be expected, even if the presence or absence of the factor gave perfect discrimination between individuals with the cystic fibrosis gene and other individuals. The factor has also been demonstrated in cell-free media in which fibroblasts grown from amniotic cells derived from foetuses believed to be heterozygous, has also been reported.

Thus the results indicate that the basic biochemical defect characteristic of cystic fibrosis, and presumably responsible for the abnormal production of the factor, is detectable under conditions which would allow prenatal diagnosis. But so far satisfactory discrimination between homozygous individuals affected with cystic fibrosis and healthy heterozygous carriers on the basis of production of the factor has not yet been achieved. Such discrimination would of course be a necessary prerequisite for prenatal diagnosis. Also the biological assay systems at present available for detecting the factor are far too difficult and precarious for diagnostic use in a routine manner.

It is a plausible hypothesis that the cystic fibrosis ciliary factor is a substance which in the normal homozygous individual is rapidly degraded or inactivated by the action of some enzyme or inhibitor, and that the basic defect in cystic fibrosis and in heterozygotes is a deficiency of this enzyme or inhibitor of sufficient degree to result in accumulation of the factor. Research aimed at identifying this postulated enzyme (or inhibitor) of the cystic fibrosis factor is actively being pursued and if successful would quite probably open the way to the development of methods for the identification and discrimination of foetuses homozygous and heterozygous for the

cystic fibrosis gene by direct biochemical assays on amniotic fluid cells grown in tissue culture.

Since the prognosis is generally so poor and the incidence of the condition is so high, the development of a satisfactory method of prenatal diagnosis with the possibility of the abortion of foetuses found to be affected, is likely to lead to a requirement for a not inconsiderable expansion of the facilities for this type of work. If 'high risk' pregnancies were only recognizable by a previous birth of a child affected by cystic fibrosis, this requirement would be limited by the fact that only a small proportion of all possible 'at risk' pregnancies would fall into this category. Nevertheless, the number involved would still make an appreciable difference to the total prenatal diagnoses being undertaken.

However, it seems likely that if a satisfactory procedure for prenatal diagnosis by, for example, enzyme assay were to be developed, then the new knowledge would quite probably also lead to the development of suitable methods for detecting heterozygotes in the healthy adult population. If so, the question would arise as to whether population screening for heterozygotes should be carried out so that 'high risk' pregnancies could be identified prior to the birth of a child with cystic fibrosis. This would not only result in the need for further expansion of prenatal diagnosis facilities, but would also require the setting up of a major programme for the population screening for heterozygotes.

Haemoglobinopathies

Recent work in the USA has opened up the possibility that within perhaps a few years satisfactory techniques, capable of obtaining the prenatal diagnosis of conditions such as sickle cell anaemia and β-thalassaemia before the twentieth week of gestation, may well become available for widespread application. The significance of such a possibility lies in the very high incidence of these conditions in particular populations; sickle cell anaemia among people in Africa or whose ancestors came from Africa, β-thalassaemia in populations in the Mediterranean area and the Middle East. Both conditions are an important source of morbidity and mortality in children of these ethnic groups.

The prenatal diagnosis of such conditions presents unusual

problems. Both sickle cell anaemia and β-thalassaemia represent inherited abnormalities in the synthesis of the β-polypeptide chain of haemoglobin, and their prenatal diagnosis requires the analysis of haemoglobin formed in red blood cells of the foetus. Amniotic fluid cells do not synthesize haemoglobin and so can provide no information. Thus a safe procedure for obtaining a sample of foetal red cells is a prerequisite.

Another problem arises from the fact that while the predominant haemoglobin present in red cells in post-natal life is so-called adult haemoglobin or HbA, which is made up of two β-polypeptide chains and two α-polypeptide chains (ie $\alpha_2\beta_2$), the predominant haemoglobin formed in foetal life is so-called foetal haemoglobin which is made up of two γ-polypeptide chains and two α-polypeptide chains (ie $\alpha_2\gamma_2$). Only a very small proportion of the haemoglobin formed in the foetus is HbA containing β-chains. But the prenatal diagnosis of both sickle cell anaemia and β-thalassaemia can only be made by demonstrating the specific abnormalities which occur in β-chain synthesis, since the synthesis of α- and γ-chains which are the principal polypeptide chains formed in the foetus are not directly affected.

Methods by which suitable blood samples can be obtained directly from placental blood vessels with the minimum of trauma are currently being worked out and preliminary results suggest that a satisfactory and safe procedure can probably be developed (18). The blood samples may evidently contain both foetal and maternal red cells, but because the rate of haemoglobin synthesis is much more active in the foetal than in the maternal red cells, it seems that a satisfactory analysis of β-chain synthesis by the foetus is nevertheless feasible (19). This analysis involves the incubation of the blood sample with a radioactively labelled amino acid and the subsequent separation by chromatography of the labelled polypeptide chains which are synthesized. Experiments carried out on blood samples from abortuses suggest that the prenatal diagnosis of sickle cell anaemia and probably also β-thalassaemia can indeed be made by this general procedure prior to the twentieth week of gestation. These procedures are still, however, at the very earliest stages of development and there is still a long way to go before they will be ready for widespread practical application.

But the general feasibility of the approach does appear to have been established.

Sickle cell anaemia and β-thalassaemia are both inherited as autosomal recessive diseases. However, unlike the situation for most conditions inherited in this way, sensitive and reliable procedures for the detection of heterozygotes by population screening have been established, particularly with respect to the sickle cell gene. They have indeed been widely applied in surveys of populations in many different parts of the world. As a result a great deal is known about the frequencies of the abnormal genes concerned in various populations and ethnic groups.

Because practical methods for the detection of heterozygotes are already available, and because of the high incidence of such heterozygotes in particular ethnic groups, one may expect that if prenatal diagnosis of these conditions becomes possible, then the selection of 'high risk' pregnancies will largely come to depend on population screening in order to identify couples both of whom are heterozygous.

It is apparent, however, that any attempt to provide prenatal diagnosis for such conditions would raise new organizational and practical problems of a very considerable magnitude. It so happens that the incidence of these particular diseases is greatest in relatively underdeveloped countries. The introduction on any widespread basis of what would inevitably be a highly sophisticated set of procedures, seems a quite remote possibility in areas where the available health services are already over-burdened and often incapable of dealing for purely economic reasons with major medical problems on which considerable inroads could in principle be made by improvements of an essentially much simpler nature. So the widespread application of the highly sophisticated techniques of prenatal diagnosis is likely to have a very low priority for many years to come.

Even in more advanced countries with relatively well-developed health services, the introduction of prenatal diagnosis for conditions such as sickle cell anaemia and β-thalassaemia would raise formidable problems. In the USA, for example, it has been estimated that the incidence of heterozygotes for the sickle cell gene in the Black segment of the population is about 1 in 25, and that about 1 in 625

new-borns in this very large ethnic group may suffer from sickle cell anaemia (20). In addition there is probably a similar incidence of related disorders such as sickle cell-haemoglobin C disease and sickle cell-β thalassaemia. The numbers of pregnancies 'at risk' are clearly very considerable.

Even in England where the number of people who have come, or whose ancestors came, from parts of the world with high frequencies of these genes is proportionately very much less, the actual numbers of pregnancies 'at risk' are quite appreciable. An illustration of this problem as it occurs in a particular community is provided by the results of a study of the Cypriot population in three boroughs of north London, which suggested that about 1 in 7 are heterozygous for a β-thalassaemia gene, and that about 0·5 per cent of the new-born may be expected to suffer from β-thalassaemia major (21).

Genetic linkage and prenatal diagnosis

There is currently a great deal of research in progress, which has the aim of mapping the positions of different genes on the human chromosomes. Such 'linkage' information could, in certain circumstances, prove useful in the prenatal diagnosis of abnormalities which cannot be identified by specific biochemical tests. It is likely to be of most use for autosomal dominant and X-linked diseases, though even here its application to particular conditions will, by its very nature, be restricted to a relatively small fraction of the pregnancies 'at risk'.

Genes which happen to lie close together on the same chromosome are said to be 'linked'. They tend to be inherited together because they are less frequently separated by 'recombination' or 'crossing-over' at meiosis, than genes which lie far apart on the same chromosome or are on different chromosomes, which recombine freely and are therefore inherited independently.

The phenomenon of 'linkage' may be useful in prenatal diagnosis if it so happens that the chromosomal locus at which the gene determining the abnormality in question occurs, is closely linked to another locus at which there are two or more alleles occurring commonly in the normal population, whose distinctive effects can be clearly identified both in the parents and other members of the

family, and also in the foetus by studies on amniotic fluid cells, or the amniotic fluid itself. Such common allelic variants are often referred to as 'genetic markers'.

To be useful in, for example, an autosomal dominant condition it is necessary that the parent who is heterozygous for the gene causing the particular abnormality must also be heterozygous for two of the alleles at the 'marker' locus. Maximum information is obtained if the other parent is homozygous at both the loci, and also if it is possible to carry out tests for the 'marker' alleles in the parents of the doubly heterozygous parent (ie the grandparents of the foetus, one of whom will usually have the abnormality in question) and also on other members of the family, so that what is known as the 'phase' of linkage can be determined from the pedigree.

It is apparent that the requirements are quite stringent and can only apply to a fraction of the pregnancies 'at risk' for the particular abnormality. Even in these cases the information produced by prenatal studies can usually only provide a probability estimate that the foetus will or will not be affected, and this will depend on the magnitude of the 'recombination fraction' which will have been previously determined. Thus, if the 'recombination fraction' is known to be 10 per cent, then at best one would only be able to say in the case of an autosomal dominant abnormality that there is a 90 per cent chance of the foetus being affected, rather than the ordinary 50 per cent chance. The necessary calculations to arrive at these probabilities from the information provided by the pedigree studies can be quite complex. A further complication is that very often the magnitude of the 'recombination fraction' differs according to the sex of the doubly heterozygous parent.

Myotonic dystrophy is one autosomal disease where it has been suggested that this type of analysis is potentially useful in prenatal diagnosis (22). The condition cannot yet be identified prenatally by specific tests on amniotic fluid cells grown in tissue culture. However, it has been shown that the chromosomal locus at which the gene determining this condition occurs, is closely linked to the so-called 'secretor' locus at which two common alleles are found in the general population (23). These alleles determine

the so-called 'secretor status' of an individual, that is whether his secretions (such as saliva) contain or do not contain substances with the A, B, or H blood group antigenic specificities. The distinction between whether a foetus is an 'ABH secretor' or an 'ABH non-secretor' can be made by appropriate tests on the amniotic fluid (24).

So far only one example of the application of this general principle to a particular pregnancy has been reported (25). Here the family studies showed that the mother who was affected with myotonic dystrophy was an 'ABH secretor' and was heterozygous at the 'secretor' locus with the 'non-secretor' and the 'myotonic dystrophy' genes in coupling. The father who had the 'ABH secretor' phenotype could have been either heterozygous or homozygous. If the foetus had been found to be an 'ABH non-secretor', then there would have been about a 90 per cent chance that it also carried the dystrophia myotonica gene, and if so the parents wished to have it aborted. In fact, the foetus turned out to be an 'ABH secretor' and so the pregnancy went to term. Since dystrophia myotonica is not recognizable in childhood, it is not yet known whether the child actually had the abnormal gene or not.

As yet there are few other conditions which might be regarded as suitable candidates for selective abortion, which cannot be diagnosed by a specific test on amniotic fluid cells, and for which there is linkage information which might be a useful guide in particular pregnancies. One example is the X-linked condition haemophilia A which has been shown to be closely linked to the gene locus determining the enzyme glucose-6-phosphate dehydrogenase (26). In Black populations three common alleles occur at the glucose-6-phosphate dehydrogenase locus and their distinctive enzyme products can be identified in tissue-cultured amniotic fluid cells. Some 40 per cent of Black women in the USA and a somewhat greater proportion in Africa are recognizably heterozygous at the glucose-6-phosphate dehydrogenase locus, so that certain pregnancies in Black women thought to be at risk for haemophilia might, in principle, be monitored in this way.

3

Effects on the incidence of genetic disease

The immediate effect of prenatal diagnosis and the selective abortion of foetuses with particular abnormalities is to reduce the incidence of such abnormalities among the liveborn. The question arises as to what the magnitude of this reduction is likely to be, assuming that the methods of prenatal diagnosis which have so far been shown to be practical become more widely applied, and what further changes may be anticipated as new techniques applicable to other conditions become available. Since the consequence of selective abortion is to eliminate individuals with particular genes or chromosomal abnormalities, one may also wonder what the long-term implications may be for the genetic make-up (the so-called 'gene-pool') of human populations in which such procedures become widely practised.

In general, different consequences can be expected to follow from selective abortion according to whether the particular condition is determined by an abnormality of a single gene, or is due to a gross chromosomal abnormality, or belongs to the less clearly defined group of disorders and malformations which are regarded as multifactorial in origin. And where the condition is attributable to the abnormality of a single gene, different effects may be expected according to whether this is located on one of the 22 autosomal chromosomes or on the X-chromosome, and on whether the pattern of inheritance of the disorder is 'recessive' or 'dominant'. Each of these different categories of condition must therefore be considered separately.

AUTOSOMAL RECESSIVE CONDITIONS

A very large number of different conditions inherited as autosomal recessives are already known to occur, and new examples are

See references on p. 98.

constantly being identified. The majority of these diseases are extremely rate, with incidences varying between perhaps 1 in 100,000 and 1 in a million births. But in any particular population a few severe conditions inherited in this way may occur significantly more frequently. For example in populations of European origin, cystic fibrosis occurs in about 1 in 2,500 births and phenylketonuria in about 1 in 15,000 births.

Although exact figures for the incidence of the many different severe autosomal recessive conditions are not available, it seems that one or another of them may be present in roughly 1–3 per 1,000 of all newborn. This is a not inconsiderable number when viewed in terms of the population as a whole. At present of course techniques for prenatal diagnosis are available for only a small proportion of these conditions, but no doubt the range of such techniques will increase progressively.

The essential point about the genetics of disorders of this type is that the affected individuals receive the abnormal gene from each of their parents. Heterozygotes who have received the abnormal gene from one parent and its normal counterpart or allele from the other are quite healthy, and most of the abnormal genes which occur in the population are present in such healthy heterozygous carriers. The incidence of these healthy heterozygous carriers can be approximately estimated as twice the square root of the incidence of affected patients. Thus for an autosomal recessive disease such as galactosaemia with an approximate incidence of perhaps 1 in 75,000 births, about 1 in 140 individuals in the general population may be heterozygous for the abnormal gene involved, and for a condition such as cystic fibrosis with an approximate incidence of 1 in 2,500, as many as 1 in 25 of the population may be heterozygous carriers of the gene. It will be apparent that the healthy heterozygotes greatly outnumber the affected patients.

The great majority of affected patients are the children of healthy parents both of whom are heterozygous. Consequently the effect of prenatal diagnosis and selective abortion on the incidence of the disorder will depend on how pregnancies 'at risk' are identified.

In theory if all matings between heterozygotes could be identified by some screening programme, and if each of the pregnancies

so identified was subjected to prenatal diagnosis with the selective abortion of the 25 per cent of foetuses found to have the disorder, then the condition would be effectively eliminated from the next generation. But it should be noted this general programme would need to be repeated in successive generations, since the abnormal gene itself would not have been eliminated. In fact, as will be discussed later, its frequency is if anything likely to increase.

Such a programme would require a satisfactory method for the detection of heterozygotes and its application to all prospective mothers and also to the spouses of such women found to be heterozygous. For a variety of reasons this can hardly be envisaged in the foreseeable future as a practical approach for the great majority of rare recessive diseases. It will no doubt only be considered for the relatively small number of conditions which happen to have an appreciable incidence so that the heterozygotes constitute a significant fraction (say more than 2–4 per cent) of the population. Even here the practical difficulties involved and the resources required are likely to be formidable.

For most autosomal recessive conditions therefore, pregnancies 'at risk' will continue to be identified because of the previous birth of an affected child. Consequently a much more modest reduction in the incidence of a particular disorder is to be expected from selective abortion. The magnitude of this will depend on such factors as the distribution of family sizes in the population, and the average age at which the particular condition tends to be recognized and diagnosed. But various calculations (1) suggest that even if all subsequent pregnancies in all families in which an affected child had occurred were monitored, the reduction in incidence of a particular condition is likely to be no more than 15–25 per cent (see Appendix 6). In practice it would probably be much less.

Natural selection

Most autosomal recessive conditions which would be judged sufficiently severe as to justify selective abortion, lead to death in early life or if they allow survival to adult life are such as to limit severely the likelihood that the affected individual will have children. Consequently the particular abnormal genes present in such individuals will either not be transmitted to the next genera-

tion, or will have a much-reduced chance of being transmitted. Thus there is a tendency for the total number of such abnormal genes in the population to be reduced by what is in effect natural selection. However, this only affects a very small proportion of the particular abnormal genes concerned, because the majority occur in healthy heterozygous carriers. In most recessive disorders this loss of abnormal genes by natural selection is thought to be counterbalanced by the appearance of new ones as a result of fresh mutations. So the frequency of the gene in the population tends towards an equilibrium in which the loss of the gene due to natural selection is balanced by fresh mutations.

In some cases where an autosomal condition is unusually common in particular populations, the high incidence of the gene may be due to the healthy heterozygotes being at a selective advantage compared with other individuals in the population, either because they have a better chance of surviving to adult life or because they are for some other reason more fertile. This phenomenon, sometimes referred to as heterosis, almost certainly accounts for the high incidence of the sickle cell gene in Africa. It seems that the sickle cell heterozygote has a better chance than the so-called normal homozygote of surviving to adult life and having children under conditions of severe endemic malaria. A similar phenomenon probably also accounts for the high incidence of β-thalassaemia gene in certain populations. It has also been postulated that the relative high incidence of the gene determining cystic fibrosis in Europe may also be due to some sort of heterosis, though in this case the nature of the postulated selective advantage for the heterozygote is quite obscure.

If heterosis occurs, the loss of the abnormal genes by the reduced reproductive capacity of the affected patients is largely counterbalanced by the increased contribution to the next generation made by the heterozygotes. If the heterozygous advantage no longer holds because of a change in the environmental circumstances (for example, in the case of the sickle cell gene or β-thalassaemia, the eradication of malaria) then the frequency of the gene will tend to decline. So the incidence of the particular disease will be progressively reduced. But because this reduction is the consequence of the operation of natural selection against the affected homozygous

individuals who carry only a small fraction of the total number of the abnormal genes in the population, the process is inevitably very slow. It may therefore be expected that many generations will elapse before the disease becomes so infrequent that the loss of abnormal genes, due to reproductive incapacity of the affected patients, is counterbalanced by new mutations. The slow rate at which natural selection operates against an autosomal recessive condition, whose incidence was once very high because of heterosis, explains, for example, the persistence of sickle cell anaemia as a common disease in Black populations in the USA.

Reproductive compensation

For autosomal recessive disorders which are of sufficient severity that the affected patients will make no contribution to the genes of the next generation, it might be thought at first sight that in population terms artificial selection by abortion is effectively the same as natural selection. However, it has been pointed out that this is not necessarily so, and that in certain circumstances selective abortion might in fact lead to an absolute increase in the number of abnormal genes in the population as a whole.

The reason for this is that since selective abortion will occur early in a pregnancy, and can be carried out against further affected foetuses in subsequent pregnancies, there will be a tendency for the affected foetuses to be replaced by normal infants until the size of the family is whatever the parents would originally have wished to have. This phenomenon, usually referred to as 'reproductive compensation', may indeed go on to some extent in families in which affected children are actually born, where the parents wish to have at least so many normal children. But because of the burden imposed by the affected children it is likely to be very much more limited in such circumstances than where the abnormal foetuses can be eliminated in early pregnancy.

But two-thirds of the healthy children born in such families will be heterozygous for the particular abnormal gene involved. So in effect, affected infants who could not in any case contribute genes to the next generation would be replaced in two-thirds of the cases by healthy heterozygotes who could. The net effect would be to

increase marginally the number of abnormal genes transmitted to the next generation.

An increase in the incidence of heterozygotes produced in this way might be expected to result eventually in increased numbers of abnormal homozygotes. The important question, of course, is what the magnitude of such an effect might be and the rate at which it might occur. This problem has attracted some interest.

The rate at which the frequency of a particular abnormal gene in the population would be expected to increase from generation to generation would of course depend on how extensively selective abortion is carried out and the manner in which pregnancies at risk are identified. It would also depend on the initial frequency of the gene in the population; on the number of normal children which families where selective abortion of affected foetuses took place would in fact aim to have; on the degree to which reproductive compensation takes place in the absence of selective abortion; and on other factors such as the mutation rate and whether any degree of heterosis is operating.

A number of calculations have been made making various assumptions about the magnitude of these factors (2). The calculations are complex but in general they appear to show that even under extreme assumptions which are quite unlikely to be achieved in practice, any increase in the incidence of affected homozygotes which might be appreciable would take very many generations to occur. The changes in incidence from this cause, in say the next hundred years (four to five generations), would evidently, according to such calculations, be very slight.

Thus the relaxation of natural selection brought about in this particular way would hardly seem to represent any serious threat to the genetic constitution of the human species taken as a whole, particularly as it may reasonably be expected that other advances in knowledge over the next century or two may well invalidate long-term projections calculated simply on the basis of what is known now.

AUTOSOMAL DOMINANT CONDITIONS

Many different inherited abnormalities apparently occurring in individuals heterozygous for a particular abnormal or mutant gene located on one of the twenty-two pairs of autosomal chromosomes are known. However, only a fraction of these are sufficiently severe as to be regarded as potential candidates for selective abortion. These perhaps amount together to about 1 per 1,000 newborn. But so far satisfactory techniques have not yet been developed to enable any of these conditions to be specifically identified *in utero,* prior to the twentieth week of gestation. No doubt appropriate methods will eventually be found, at least for some of them.

In such disorders one of the two genes present is functioning normally. This makes it more difficult to characterize the nature of the underlying abnormality in biochemical terms, as compared with the situation in autosomal recessive or X-linked disorders (3). Satisfactory methods for prenatal diagnosis by, for example, the determination of specific enzyme or protein abnormalities in tissue cultured amniotic fluid cells, are hardly likely to emerge before the key biochemical abnormalities have been identified in affected patients.

On average, one-half the children of an affected individual may be expected to receive the abnormal gene and be similarly affected. So all pregnancies from matings in which one parent has the condition will be 'at risk' and thus be candidates for prenatal diagnosis if the appropriate techniques are developed. However, because of the variability in manifestation of the clinical abnormality, which is often observed in such 'dominant' disorders, not all heterozygotes may exhibit overt clinical manifestations of the disease, and such heterozygotes would presumably need to be identified by appropriate biochemical tests among individuals who have a known family history of the condition.

Huntington's chorea is an example of a serious condition where this would inevitably be the case, and it illustrates some of the general problems which autosomal dominant disorders may be expected to pose. In most cases the overt clinical signs or symptoms of Huntington's chorea became manifest sometime between the ages of 30 and 50. The characteristic choreiform movements

become more severe over a period of years and these are very frequently associated with mental changes usually leading to a progressive dementia. Because of the relatively late age at which the symptoms of the disease develop, many of the affected patients will already have married and had children before the condition can be diagnosed. Certainly it does not appear that the effective fertility of such individuals is markedly reduced. The results of various studies suggest that the total number of children born to patients eventually diagnosed as having Huntington's chorea is at most 10–20 per cent fewer than might have been expected from data on a comparable number of healthy individuals from the same population (4).

Huntington's chorea is not as rare a condition as was once thought. Recent population surveys suggest that the prevalence of the disorder in this country may be at least 1 in 20,000 of the general population (5). Since most individuals under the age of 30 who are heterozygous for the abnormal gene will not have been identified in such studies, it seems probable that the true incidence of heterozygotes may be between 1 in 5,000 and 1 in 10,000. So it is probably one of the most common of the autosomal dominant diseases with severe consequences.

Since half the children of patients known to have Huntington's chorea may be expected to develop the disease sooner or later, the condition poses a particularly difficult problem in genetic counselling. Individuals from families in which Huntington's chorea has occurred will usually come for advice in their early 20s when, even if they carry the abnormal gene, they will usually show no evidence of the incipient development of the disease. So they are likely to be confronted with the inevitably inadequate information that they themselves are at risk for serious crippling disease, as well as there being a significant risk for any children they should have. These risks can be calculated according to the information in the family history, but they are usually not very comforting.

Despite much investigation, the basic biochemical defect in Huntington's chorea is still quite obscure. But it would perhaps not be unreasonable to expect that it might be identified in the next decade. Furthermore, it is quite conceivable that when identified this defect will be found to be demonstrable in fibroblasts

grown in tissue culture, and if so prenatal diagnosis would become a real possibility.

Clearly if such developments took place they would in the first place make it possible to detect, in families where Huntington's chorea is known to have occurred, those individuals who are heterozygous for the abnormal gene but who have not yet developed its clinical manifestations. This would at least provide reassurance about the future for those members of the family who are found not to be heterozygous, but who would previously have been regarded as being 'at risk'. It is also possible that the discovery of the abnormal biochemical process involved in the disease might lead to some form of therapy which would prevent the development of serious neurological damage, or significantly ameliorate it. In such circumstances the possibility of having normal children by prenatal diagnosis and selective abortion would no doubt be welcomed.

In the absence of such a therapeutic development which could prevent or limit the degree of eventual neurological damage, individuals found to have the abnormal gene might very well not wish to have children. But if they did, then prenatal diagnosis and selective abortion might at least offer them the chance of having children who would not be at risk in later life of developing this peculiarly disastrous disorder.

Several quite severe autosomal dominant disorders such as myotonia dystrophia, polycystic disease of the kidney and certain forms of retinitis pigmentosa, resemble Huntington's chorea in that the diagnosis may not be made until the affected individuals have already had children because of the insidious onset of the clinical manifestations, and they present the same kind of general problem. Other autosomal dominant disorders such as tuberous sclerosis and neurofibromatosis pose a different kind of problem, which arises from the variability in the severity of the clinical manifestations which are to be found from one heterozygote to another. Thus heterozygotes for a gene determining tuberous sclerosis may often be severely mentally retarded and this is apparent at an early age, but there are also other heterozygotes in which the clinical consequences of the disorder are very much less severe and indeed the condition may sometimes be hard to diagnose

because the signs of the disease are minimal. In such circumstances the discovery of a specific biochemical method for arriving at the diagnosis would be an important development and it might conceivably lead to a satisfactory technique for prenatal diagnosis. It is in fact among the less severely affected patients that such a technique would be of most practical importance, since the more severely retarded patients are in general less fertile.

The increasing use of prenatal diagnosis in pregnancies identified through family studies as being at risk for an autosomal dominant condition, and the selective abortion of the 50 per cent of foetuses found to be affected, would be expected to result in a progressive decrease in the frequency of the gene determining the disorder. But this process would not culminate in its complete elimination. This is because a proportion of all the cases which occur in any generation will be the consequence of a fresh mutation occurring in the germ line of one or other of the parents. Since the somatic cells of the parents would not be heterozygous for the abnormal gene, the pregnancies at risk because of a fresh mutation would not be identifiable.

The proportion of cases attributable to fresh mutations varies from condition to condition. In general this proportion is greater in conditions where the reproductive capacity of the affected individuals is on average severely reduced, and it is smaller where the effective fertility of affected individuals compared with that of other members of the population is only reduced a little. For example, family and population studies suggest that for tuberous sclerosis the proportion of cases due to fresh mutations may be 50 per cent or more (6). This would represent the maximum degree to which the incidence of the condition could be reduced if a completely effective programme of case detection and selective abortion were in operation. In the case of Huntington's chorea a more drastic reduction might in theory be achieved, because here it seems probable that a much smaller proportion of cases are the products of fresh mutations (perhaps 10 per cent).

X-LINKED ABNORMALITIES

Many recessive diseases due to abnormal genes located on the X-chromosome have been recognized because of the very characteristic pedigrees which occur. The disease affects males who have the abnormal gene on their single X-chromosome. It is transmitted to them from their mothers who, in the vast majority of cases, are symptomless heterozygotes. Some X-linked abnormalities, such as the forms of glucose-6-phosphate dehydrogenase deficiency which are common in African and Mediterranean populations, are hardly sufficiently serious in their clinical concomitants to be regarded as candidates for selective abortion. Most of the more serious disorders are individually very rare, though one or another of them probably occur in perhaps 2–4 per 1,000 new-born males.

The problems involved in identifying pregnancies 'at risk' for such conditions have already been mentioned (pp. 19–24). It has also been noted that because of the peculiar pattern of inheritance selective abortion can be carried out even in the absence of a specified method of prenatal diagnosis, provided one is prepared to abort the normal male foetuses as well. Clearly where the affected male foetuses can be specifically identified, as is the position in a few X-linked abnormalities such as the Lesch-Nyhan syndrome and Fabry's disease, this is a more desirable procedure.

Selective abortion, as has already been mentioned, is likely to lead to reproductive compensation. And, as in the case of autosomal recessive diseases, it will tend to result in an increased frequency of the abnormal gene in succeeding generations. This would mean an increase in the absolute number of female heterozygotes and a corresponding increase in the number of pregnancies at risk. Calculations have been carried out to assess the likely magnitude of this effect making various assumptions about the manner in which pregnancies at risk are identified, and the general pattern of reproduction in the population. The outcome is also affected by whether the selective abortion procedure would involve elimination of all male foetuses, or would involve only those with the specific abnormality. The various other factors mentioned with respect to the increase in heterozygotes as a result of reproductive

compensation for autosomal recessive conditions (p. 51) also need to be taken into account.

The results of these calculations indicate that the rate of increase in the frequency of the abnormal gene is likely to be very much greater for X-linked recessive abnormalities than for autosomal recessives (7). Indeed if rather extreme assumptions are made about the mode of application and the extent of a selective abortion programme directed at an X-linked recessive abnormality, the calculations suggest that in certain circumstances the incidence of the female heterozygotes might be doubled in two or three generations. But the assumptions are somewhat unrealistic and it seems quite unlikely that the rate of increase in the incidence of heterozygotes would in practice be anything like as marked as this.

As with autosomal dominant abnormalities the amount by which the incidence of a sex-linked disorder might in theory be reduced, by the widespread selective abortion of affected foetuses, is limited by the rate of occurrence of fresh mutations. In conditions which are sufficiently severe as to result in death in childhood or completely prevent reproduction if survival to adult life occurs, then one may expect on theoretical grounds that one-third of all the affected cases in any one generation will be attributable to fresh mutations. So this sets a limit to the extent by which the incidence of the disease might be theoretically reduced. Where affected patients make some contribution to the next generation (for example, in haemophilia) the fraction of cases attributable to fresh mutations will be proportionately less, so that in theory a greater reduction in incidence of the disorder might be achieved.

CHROMOSOME ABNORMALITIES

Most of the severe abnormalities due to chromosomal aberrations, which may be regarded as appropriate for selective abortion, occur sporadically. In formal terms they can be regarded as fresh mutations which are the consequence of some more or less randomly occurring events in the course of gametogenesis in one or other of the parents. There are of course exceptions to this generalization, notably in the case of certain translocations (see pp. 15–17), but apart from these exceptions, pregnancies at risk

for chromosomal abnormalities resulting in a severe defect cannot be identified by chromosome studies on the parents.

Nevertheless it would in theory be possible to eliminate effectively all cases of chromosomal abnormality from the population. This would require that amniocentesis was performed in all pregnancies and chromosomal analysis carried out on the amniotic cells after tissue culture. Such an approach is already at least in principle technically feasible, and indeed has on occasion been advocated (8). Severe abnormalities due to chromosome aberrations probably occur in slightly less than 2 per 1,000 live births. So such a programme would imply that for every affected foetus identified and aborted at least 500 unaffected pregnancies would need to be subjected to amniocentesis.

It does not appear likely that this type of massive programme for the elimination of this class of abnormalities would be generally considered as acceptable in the immediate or even the foreseeable future. Quite apart from the considerable practical problems involved in mounting and maintaining such a programme and the resources which would be required, there would seem to be too many uncertainties about the possible long-term consequences for the chromosomally normal foetuses and also for the mothers. Information about possible harmful consequences which might ensue from amniocentesis is still very limited. It seems from the available data that they are sufficiently small to be tolerable in selected pregnancies where there is a relatively 'high risk' of an abnormal foetus being present. But even very slightly harmful and, at present, undetected effects would inevitably be magnified by the application of the procedure to all pregnancies, and it is not as yet possible to assess what the total effect might be.

So for the present, prenatal diagnosis and selective abortion of chromosomal abnormalities is likely to remain largely restricted to so-called 'high risk' pregnancies, though no doubt what is judged to represent a 'high risk' may vary from place to place.

Most amniocenteses for chromosomal abnormalities are carried out, and no doubt will continue to be carried out, in older mothers because of the increased risk of mongolism and also other trisomic abnormalities. Table 2 (Chapter 2) suggests that if amniocentesis of all pregnancies in women over the age of 40 had been carried

out in this particular population (England and Wales, 1970), about 16·7 per cent of cases of mongolism among the live-born might have been eliminated. This would have involved carrying out the procedure on about 1·74 per cent of all pregnancies. If the procedure had been extended to women over the age of 35, a further 18·4 per cent of mongols might have been eliminated, though this would have involved carrying out amniocentesis on nearly four times as many pregnancies (6·1 per cent of the total). Thus, in all, some 35 per cent of all mongols might have been eliminated by confining the procedure to less than 8 per cent of the total number of pregnancies. A similar reduction in the incidence of other trisomic abnormalities in the live-born would also have been brought about at the same time.

The proportion by which the number of live-born infants with these particular abnormalities may be reduced by amniocentesis and selective abortion in older women, will of course depend on the distribution of maternal ages in the population at any particular time. There is at present a tendency for the average age at which women have their children to be falling, mainly due to reduction in average family size and an associated reduction of pregnancies in older women. This change in social custom, if it progresses, should in itself tend to reduce the incidence of chromosomal abnormalities in essentially the same way as is produced by amniocentesis and selective abortion deliberately applied to older women. It would thus tend to remove one of the major indications for prenatal diagnosis as presently carried out.

Less than 5 per cent of patients with mongolism represent unbalanced translocations, but in fewer than half of these is a corresponding balanced translocation present in one or other parent (see pp. 15–17). The remainder occur sporadically, presumably as a result of a fresh 'mutational' event giving rise to the abnormal translocated chromosome in the gonads of one of the parents. So an extensive screening programme to detect the healthy 'translocation carriers' and hence the pregnancies at risk would only marginally influence the number of mongol infants born. However, there is obviously a good case for screening as extensively as possible the relatives of individuals identified as 'translocation carriers' through the birth of a mongol with an 'unbalanced translocation' (see for

example Chapter 2, Fig. 1, pp. 16–17). This could lead to the identification of pregnancies with a 'high risk' prior to the birth of a mongol child.

As in the case of autosomal and X-linked recessive abnormalities reproductive compensation in families where selective abortion is applied, because one of the parents is a 'translocation carrier', is likely to occur. However, the increased population incidence of 'translocation carriers' in later generations from this cause is likely to be small.

'MULTIFACTORIAL' ABNORMALITIES

Some 1–2 per cent of all new-born infants have a severe congenital abnormality such as anencephaly, spina bifida, malformation of the heart, cleft palate, club foot, etc., the causation of which is quite obscure. Most of these conditions show an increased familial incidence, the risk to further sibs after the birth of an affected infant varying between about 2 and 5 per cent for the different conditions. Both genetic and environmental factors are probably involved in the causation of these different abnormalities, but little is known about the precise nature of these factors or how they may interact.

Where, as in the case of anencephaly and 'open' spina bifida, a method of prenatal diagnosis can be developed, then selective abortion will reduce the incidence of the abnormality among the live-born. The extent of this reduction will, of course, depend on how far pregnancies 'at risk' can be identified, and the precision of the technique of prenatal diagnosis.

The possibilities of prenatal diagnosis of the neural tube defects are currently being actively investigated and it is difficult to predict what the final outcome will be, though it is already clear that some reduction in the incidence of these conditions among the live-born will be achieved. Whether this could lead to any long-term change in the population distribution of the genetic factors that may be determinants of these conditions is, however, altogether obscure.

At present a satisfactory approach to the specific prenatal diagnosis of other types of congenital abnormality does not appear to be on the horizon, though it is conceivable that such techniques as foetoscopy (9) which involves direct visualization of the foetus

might eventually be developed to a state where they could be useful in some types of case.

Environmental factors would appear to be important in deciding why one foetus rather than another develops a particular congenital malformation of this general type. At present the nature of such environmental factors is very uncertain though many suggestions have been made in relation to particular abnormalities. If, however, they could be identified with certainty, then it might emerge that relatively simple alterations in a pregnant woman's immediate living conditions, or her diet, could greatly reduce the risk of some of these malformations occurring. Quite possibly an environmentalist approach of this kind will provide the way to reducing the incidence of this class of conditions in the future.

4

The question of ethics

Much has been written about the morality of abortion, and there is little point in my attempting to review the many different ethical, theological, and other arguments which have been advanced, even if I were competent to do so, which I am not. These arguments have a long and complex history, and they have led to widely diverging conclusions even among people who on most other major issues may find little to disagree about.

It is clear of course that if one takes the absolutist position that under any circumstances abortion is morally indefensible, then prenatal diagnosis aimed at the selective elimination of genetically abnormal foetuses can have no place in medical practice. This is so even if one accepts the slight dilution of the position which would allow the morality of abortion if the life of the mother is at grave risk by allowing the pregnancy to continue, so that there is only in effect a choice between the life of the foetus and the life of the mother.

Among human geneticists such a position has been most forcibly argued by Lejeune (1), the discoverer of the chromosomal basis of mongolism. The essential point of his argument is that once an ovum has been fertilized it has become a human being in its own right and the deliberate elimination *in utero* of the young foetus which develops from it is just as much an act of homicide as its deliberate elimination in post-natal life would be. The fact that studies following amniocentesis may lead to the certain conclusion that the foetus will inevitably develop into a grossly abnormal infant, who will die in early or later post-natal life in an extremely unpleasant manner, or may if he or she survives suffer from severe mental or physical handicap, is considered irrelevant. Such foetuses he argues have an equal right to life as other foetuses, and should be equally protected.

The argument focuses attention solely on the foetus, and does not allow any other considerations such as the welfare of the

See references on p. 99.

mother, the welfare of other immediate members of the family, or the welfare of society at large, to be taken into consideration in arriving at the decision. Nor, in giving primacy to the right to life of the particular foetus concerned, is it prepared to consider the rights of others who are 'yet unborn' and not yet even foetuses, and who may not come to be born precisely because of the birth of the foetus in question, simply because the birth of a grossly abnormal infant may impose too much burden on the mother (2).

Lejeune's position appears to be identical with the orthodox Roman Catholic position. But he has been careful to avoid making his stand on the basis of religious doctrine, as is illustrated by the following short extract (3):

I would come to very simple points now. When we discuss problems concerning adults and children, the National Institutes of Health is quite generally preferred. But when dealing with tiny fellows, especially the not-yet-born, the National Institutes of Death finds some supporters. The reason for this divergence seems to lie in the question: Are they human or not? If already human, help and heal is the goal. If not yet human, discard and destroy is the solution. . . . My personal feeling is that we should elaborate our decision on scientific grounds . . . using all the scientific information we can gather.

Let us take the example of trisomy 21, observed by amniocentesis. Looking at the chromosomes and detecting the extra 21 we say very safely 'The child who will develop here will be a trisomic 21'. But this phrase does not convey all the information. We have also seen all the 46 other chromosomes and concluded that they were human, because if they had been mouse or monkey chromosomes, we would have noticed. Hence genetically speaking we have got two answers: first, here is a human being developing; second, he is affected by trisomy 21. All the discussion springs from the fact that some people note only the extra chromosome, and others look at the whole set.

I have never believed myself the ensoulment theories (whether theological or materialistic), pretending that the developing thing *in utero* will become a man—some day, but is not yet human before a given step has been reached. Indeed this given step varies from specialist to specialist. But that is not the question. What seems obvious to me, from all we know about genetics, is simply this: if a fertilized egg is not by itself a full human being, it could never become a man, because something would have to be added to it; and we know that does not happen.

Other human geneticists are as well aware as Lejeune of the cytogenetic facts about trisomy 21, though he knew them first. But the majority do not agree with him about the conclusion to which they lead. And this is not because they have repressed the knowledge that they are looking at human chromosomes and not at mouse or monkey chromosomes. It is essentially because they are not prepared to agree that the foetus is the only one to be considered in making the decision. There are other components in the equation, particularly the well-being of the mother and other members of the family who will be affected by the birth of the abnormal child. The over-all good is in their view the ultimate arbiter, and they do not consider that it is inherently immoral to abort, for example, a mongol foetus. If this is to be counted as homicide, then they regard it as an ethically acceptable form of homicide.

Thus on the question of the morality of abortion in general and its implications for the management of pregnancies where there is a clear risk of an abnormal foetus, there is a sharp dichotomy of view and each side must go its own way.

But for those who do not accept that abortion *per se* is inherently immoral, this does not entirely dispose of the ethical issues. This is because one is considering the selective abortion of foetuses with genetically determined abnormalities, and the selective element in the procedure can pose special questions which do not necessarily arise in arguments about abortion in general.

Before considering some of these questions, it is perhaps worth pausing to note the quite remarkable changes that have occurred during very recent times in moral attitudes towards abortion in general. In this country, and in most parts of the USA, the ethical attitudes towards abortion of the medical profession and other leading sections of established society seem to have undergone an almost complete reversal of what they were just one or two generations ago. This is a quite revolutionary rate of change for a set of principles which previously were widely thought to be an immutable feature of society. These changes have been ratified by alterations in the law, which make abortion a legal operation in a wide variety of circumstances which not very long ago would have scarcely been countenanced. But the legal changes are only a

reflection of widespread changes in ethical views, and these in turn are consequences of deep rooted social changes.

The dramatic changes in moral attitudes which have occurred can be understood on the view that the system of ethics which dominates a society at any particular time is ultimately a reflection of its social structure, its economic framework, and its past history. In times of social stability moral principles may appear eternal and unchanging, while in times of social upheaval they will be increasingly questioned and indeed may become drastically altered. To account for the rapid changes which have occurred in terms of the view that morality is based on a set of absolute truths which are or should be self-evident, and which are ultimately derived from divine authority, or alternatively are instinctive in the human species, is more difficult. It would seem to require some hypothesis of demonic possession.

At present it appears that the annual number of legal abortions in this country is about one for every seven live-births. And it is therefore clear that the total number of abortions which are carried out for other reasons could only be very marginally affected by the number of abortions which might be undertaken to eliminate foetuses found by prenatal diagnosis to have some major genetically determined abnormality. The same is true for other countries where liberal abortion laws exist. It is also no doubt the case in many Catholic countries, where most abortions are carried out outside the law, but are nevertheless thought to be very numerous and often perhaps not very different in number to the total live-births.

It is perhaps fortuitous that the series of discoveries which led to the development of the techniques of prenatal diagnosis happened to be made at a time when social changes were already bringing about major alterations in abortion laws. If the key discoveries had been made twenty or thirty years earlier we would probably not have witnessed the almost explosive development of the subject, which took place almost from its inception.

The rapidity with which moral views about abortion in general have changed, swept aside much of the resistance that might have been expected to develop against prenatal diagnosis and selective abortion. So much so, that just a very few years after the first

introduction of the procedure a leading geneticist could make the following remarks in opening a symposium on 'Advances in Human Genetics and their Impact on Society' at the American Association for the Advancement of Science (4):

> In the Symposium to follow there is some discussion of the ethical issue of therapeutic abortion to prevent severe genetic disease. Actually, public acceptance of abortion as a means of birth limitation and as a right of the individual pregnant woman is now so widespread that a discussion of reservations about therapeutic abortion seems almost anachronistic.

However, even though the ethical issues surrounding the question of abortion in general may have been effectively resolved for most of those concerned with genetically determined abnormalities, this does not completely release them from the ethical hook. This is because of the moral questions which arise precisely because the procedure is aimed at being selective. In fact once the possibility of abortion for such conditions is allowed, a whole Pandora's box of new ethical problems is opened up. The absolutist position of a complete refusal to consider abortion, fortified by the appropriate religous faith, is probably the easier path to take. But who said that things have to be easy?

GRADATIONS OF SEVERITY

Perhaps the most immediate problems arise from the fact that there is an enormous range of variation in the severity of the genetically determined abnormalities which can already be identified by prenatal diagnosis, or which are likely to become so before very long.

In fact, the issues only seem clear and straightforward when the contemplated abortion involves a foetus which it is known from prenatal diagnosis will, if not aborted, suffer from a major abnormality inevitably leading to death in early post-natal life; for example Tay-Sachs's disease or the Lesch-Nyhan syndrome.

The same is generally true for conditions in which the clinical abnormality has a slower and insidious development resulting in progressive handicap, but often not leading to death till adolescence, early adult life, or perhaps later. An example is Duchenne's

muscular dystrophy. Here the severe and progressive disablement of the patient, and the impact on the family who must support the burden, seems more than sufficient to justify selective abortion. In this particular example the moral position is perhaps somewhat weakened by the fact that there is as yet no specific diagnostic test applicable prenatally, but because the abnormality is X-linked selective abortion is feasible though only at the expense of also aborting unaffected male foetuses. This, however, would almost certainly be morally acceptable to most families and their advisers faced by the problem, because of the eventual severity of the condition itself and its protracted course.

There is also for most people no moral difficulty about selective abortion for conditions which are inevitably associated with severe mental or physical handicap. Mongolism is the prime example, both because of its relatively high incidence and because of the very gross degree of mental retardation which is its characteristic feature. It is true that mongol children and adults frequently appear to be happy and contented individuals, despite the restrictions inevitably imposed on the life they can lead by their marked mental handicap. But the prolonged burden they represent for the mother and other members of the family, the difficulties about their continuing care as they grow older and their parents die or are less able to look after them, and the fact that prenatal diagnosis and selective abortion at least in some cases may offer the opportunity of their being replaced in the family by a subsequent normal child, are for most people sufficient justification for selective abortion. It should be noted that the happy and contented disposition often seen in mongol children appears to be rather special to this condition, and is not necessarily or even usually seen in other children with the same degree of retardation who in consequence may appear much less contented with their lot. In some cases of course the degree of mental handicap is such as to impose a virtually vegetable existence.

At present there are for the various conditions mentioned above, no specific forms of therapy available which make a significant impact on the severity or rate of progression of the disease. In some cases, for example Tay-Sachs's disease and mongolism, it seems unlikely from what is known about the pathology of the conditions that a really effective therapy will ever emerge. In other cases,

for example the Duchenne form of muscular dystrophy, it is by no means inconceivable that some specific form of treatment may eventually be developed which would effectively prevent further progression of the condition once it is recognized, or at least retard its progress to a sufficient degree as to make a normal or near normal form of life possible.

But there are other genetically determined abnormalities which previously inevitably resulted in a severe disability but for which there are now effective forms of treatment, though the effectiveness usually depends on careful management over long periods and perhaps indefinitely. If prenatal diagnosis is already technically feasible, or will in the future become so, decisions will have to be made as to whether selective abortion is justified.

This is perhaps already the situation in the case of the rare disorder galactosaemia which if left untreated results in a severe clinical syndrome characterized by liver damage, mental retardation, lens cataracts, and usually death in childhood. Effective treatment requires early diagnosis in the immediate post-natal period and the indefinite adherence to a galactose-free diet, which in practice mainly means a diet free of milk and many milk products. Prenatal diagnosis can be achieved by a specific enzyme assay on amniotic cells grown in tissue culture. Pregnancies at risk can at present, however, only be identified by the previous birth of a galactosaemic infant.

No doubt whether the mother would wish to ask for amniocentesis and selective abortion in subsequent pregnancies after the birth of a galactosaemic infant will depend very much on her experiences with the handling and care of the first affected infant, and these in practice might for many reasons vary widely. And presumably in the few cases of this sort that have already come up for assessment, the mother's previous experience has determined the final decision. Clearly, however, moral conflicts may well arise in coming to such decisions, because of how such decisions might affect the feelings of security of the already existing galactosaemic child, and because of differences in emphasis which the mother on the one hand and the obstetrician or genetic counsellor on the other will allow to the various factors which weigh in making the decision.

Phenylketonuria is another, much commoner, condition for which an effective form of therapy is available and is indeed almost universally administered in this country. But the therapy is much more demanding. It requires early diagnosis in the first two or three weeks after birth before any symptoms of the disease have become manifest, and is in fact only achieved by screening all new-born infants for biochemical manifestations of the disease, a considerable operation. Treatment involves the careful administration of a phenylalanine-restricted diet, and since phenylalanine is a constituent of protein, a major part of the food intake of the phenylketonuric child has to be very different in its form from a normal diet and sharply differentiates the daily life of the child from that of other children. Also the diet must be maintained at least for some years and possibly indefinitely, and must be subject to careful control. So the whole undertaking represents a considerable effort most particularly for the mother, but also for many others.

Nevertheless the whole programme for treating phenylketonuric infants has proved remarkably successful. Until a few years ago some 0·5 to 1 per cent of all patients in mental deficiency institutions were phenylketonuric. There were many more patients also severely mentally retarded, particularly the younger ones, looked after at home. Now the situation is changing quite dramatically since the patients under treatment can be expected to live a more or less normal life, except of course for the restrictions imposed by their diet.

At present there is no way of identifying by prenatal diagnosis those foetuses who will become phenylketonuric. But if a technique of achieving this is developed, one may expect that some difficult decisions could arise since it would probably only be applicable in situations where a phenylketonuric patient is already a member of the family.

It is perhaps worth noting that the development of a satisfactory technique for prenatal diagnosis of this condition is not yet on the horizon. It would appear to require a quite novel discovery rather than a systematic development of techniques already available, since the particular enzyme which is deficient in the liver of phenylketonurics is not present in normal cells grown in tissue culture under any known conditions.

Haemophilia is another condition where progressive advances in treatment have resulted in a considerable amelioration of its severity, though it remains a serious disorder. Improved therapy has greatly extended the average life-span, and has also made it possible for haemophilic patients to live a more nearly normal life, though their range of possible activities is still quite considerably restricted by their abnormality. It is clear, however, that the severity of the condition with the treatment now available can hardly be classed with such disorders as Tay-Sachs's disease, mongolism, or even Duchenne's muscular dystrophy.

It is because of this somewhat lesser degree of severity, and also the fact that it is an X-linked abnormality for which there is no specific prenatal diagnostic test so that selective abortion also requires the elimination of normal male foetuses, that it provides a useful example for the present discussion. In justifying selective abortion it is usually claimed that the decision should be arrived at by considering the rights and welfare of the mother and other members of the family, of society at large and of the potential of the affected foetus. Generally the welfare of the mother emerges as paramount and no doubt this will also be so where the problem involves haemophilia. But in this instance one can perhaps see a little more clearly how the various interests involved may conflict and so be more difficult to resolve.

Parents who already have a haemophilic son might well feel that they would only be prepared to have a further child if it were not haemophilic, and so request amniocentesis followed by abortion if the foetus turned out to be male. Alternatively, of course, the parents may feel so happy with the haemophilic son they possess, that they are quite content to risk having another and accept the added burden on them that this would bring, particularly as there would be at least a 50 per cent chance of a quite normal son.

When it comes to weighing what have been called the 'rights of the foetus' the matter is obviously much more obscure. But if the concept means anything in practical terms, its evaluation presumably turns on an assessment of the quality of the life the foetus may eventually come to have. And even if the foetus should in fact be destined to be haemophilic, the quality of the

life he might lead would perhaps be not quite as unfortunate as in the case of many other conditions for which selective abortion is contemplated.

The so-called 'rights' of society in the matter arise because it is socially desirable to minimize as far as possible the amount of ill health in the community. If the resources available for health care and welfare are limited then it can be argued that more might be provided to cope with other problems, if the amount required for haemophilics is reduced because there are fewer of them.

Clearly in any particular case there could be a conflict between the interests of the family and of society in general about what is the most desirable course to pursue. Here the role of the family doctor, or genetic counsellor, and the obstetrician come in. In traditional medicine the doctors should only be concerned with the welfare of their patients. But in these changing times some may take a wider view of their responsibilities. They may, for example, consider that the family, even if they are not inclined to the idea, should be pressed to take advantage of the opportunity of abortion for the social good. Alternatively, a doctor's own ethical position might be such that even if he accepts the idea of aborting a foetus definitely known to be severely abnormal, he might not regard the severity of this particular condition as being of a sufficient degree, especially as there is also a 50 per cent chance of aborting a normal foetus.

Finally, there is at least the possibility that if a mother should insist on her right to have an abnormal or defective child, in a social situation where this attitude is no longer the social norm, she might find herself subsequently exposed to social pressures and stigma which she may not have bargained for. And the child also may find itself looked on as an 'unnecessary' citizen. The fear of the development of such social pressures and attitudes may seem remote at present, but some at least have argued such attitudes may well become more established as selective abortion becomes widespread (see pp. 77–79).

Moving along the path of the prenatal diagnosis of conditions of decreasing severity, one eventually comes to the problem posed by the diagnosis of an XYY foetus. Such a prenatal diagnosis in the absence of routine amniocentesis of all pregnancies will only

be made fortuitously during the course of chromosome analysis on foetal cells being carried out for some other purpose (for example the diagnosis of mongolism). This is because there is no way of telling whether any particular pregnancy is more or less likely to involve an XYY foetus. However, since the condition occurs with a quite appreciable frequency (about 1 in 1,000 births), it will certainly turn up on a regular basis as prenatal diagnosis becomes an increasingly frequent procedure. The difficulty which this condition presents largely arises from our ignorance of its natural history. There is convincing evidence (5) that it is significantly (in the statistical sense) associated with deviant antisocial behaviour, but the evidence also indicates that the majority of XYY individuals live lives which are well within the range of ordinary social behaviour, and they cannot be said to have a disease in the ordinary sense. The reason for the association between this particular chromosomal constitution and the behavioural problem where this exists is not as yet understood.

Once the prenatal diagnosis is made, and presuming that the foetus is not otherwise found to be abnormal, the mother has either to be told the facts of the matter or has to be told that no abnormality was found. An explanation of the present state of knowledge about the condition, however full, can at best hardly fail to be even more obscure to the mother than it is to the experts in the subject. Since she was in any case very conscious of the possibility of aborting the pregnancy, for whatever reason the prenatal diagnosis was originally undertaken, she might very reasonably opt for aborting the XYY foetus, even though the long-term prognosis for such an individual is as far as one can see far from bad. Under the circumstances she might feel that it is better to be safe than sorry. This is perhaps particularly so because, if she decides to go on with the pregnancy, she has then to face bringing up the child with the knowledge of his unusual chromosomal status and its ambiguous prognosis. It is easy to see that this might well in itself produce undesirable and possibly serious psychological and social consequences. If the mother is not told about the findings this latter possible complication might be avoided, if she does not eventually hear of it in some other way. But to withhold deliberately such information would seem to be an act of

paternalism of a sort which would be very difficult to justify ethically and could, if more generally adopted, result in a whole variety of serious social consequences.

At the extreme end of the spectrum one comes to the question of the ethics involved in selective abortion, where there is no suggestion of an abnormal foetus, but where the parents desire the child should be of a particular sex, and that if the foetus is found to be of the other sex it should be aborted so that they can try again. Technically the diagnosis of the sex of the foetus if amniocentesis is undertaken presents no great problems, and in fact it is a standard part of full chromosomal analysis undertaken for any other reason.

At the present time most of the professionals involved in offering prenatal diagnosis and selective abortion would not agree to carrying it out simply for this purpose. Quite apart from questions of morality, they would probably argue that although amniocentesis and selective abortion may carry very low risks of damage either to the mother or to a foetus of the wanted sex, nevertheless there are risks and it would not be justifiable to take them for an essentially frivolous purpose. They would probably also argue that because their practical resources are limited, they would not feel justified in deploying them for this purpose when they could be required to deal with other more needy cases.

Parents who want the procedure will no doubt argue that although there may be no specifically medical justification the demand is not frivolous in their own particular social circumstances, and if they are prepared to take the risks, they have the right to decide for themselves about the composition of their own family. They might fortify their argument by reference to the modern social pressure to reduce family size and suggest that this carries with it the implication that parents have a right to determine the sex of their children and the order in which the sexes are born, if this is technically feasible.

Although the majority of the medical profession may set their face against this kind of argument it is probable that at least some potential parents, who are sufficiently determined and can afford it financially, will find a way of arranging it. This is possibly already happening on a small scale, and whether or not it will

become more widespread will depend on whether professional attitudes towards it harden or become more flexible.

Possibly the issue will be overtaken by other events. Recent work on the separation of Y- from X-bearing sperm (6), raises the possibility that before long it might be practical to use such a procedure followed by artificial insemination to ensure the birth of an infant of the required sex. The whole matter may well eventually be taken out of the hands of the medical profession by the discovery of some douche capable of selectively destroying X- or Y-carrying sperm which might become available directly to the public through a pharmacist or supermarket. With the rapid advances in biological knowledge that are presently occurring this possibility can hardly be dismissed as science fiction.

In any case it is apparent that because of the continuous gradations in severity of conditions which are or will become susceptible to prenatal diagnosis, lines are going to be drawn. They may vary among different centres offering the service, and also vary between parents who wish to use it. So as prenatal diagnosis and selective abortion become more widespread there would appear, at least in theory, to be plenty of room for moral conflict.

In practice, many of those who are actually engaged in carrying out the procedure are inclined to think that the very extensive discussions and arguments about its ethical basis and morality which have taken place (7) have been conducted at an altogether too rarefied level and bear little relation to real life. They feel that a mountain is being made out of what is in practice a mole-hill. And they can point to the fact that although their consultations with their patients about her or his particular problems often require a great deal of explanation and discussion before a decision is reached, it is unusual for the general ethics or morality of the possible decision to be a major matter of concern.

In reply it could be argued that these situations are to a considerable extent self-selected because of the relatively recent introduction of the procedure and the comparatively small scale on which it is so far practised. Only those who in fact already favour prenatal diagnosis and selective abortion offer it as a service and usually they have in mind only the severer types of conditions. Similarly, only those patients who already accept in principle the

morality of the procedure will tend to consult them, and because the procedure is relatively new usually only because they are confronted with the more severe type of problem.

The situation could well change as the procedure becomes more widespread and estimating the magnitude of future problems from the current situations may lead one into failing to see the wood for the trees. However, it has to be admitted that what happens now is real life, and predictions about what may come to be, are largely guesses and speculations and could prove well wide of the mark.

THE NOSE OF THE CAMEL

Evocative phrases such as 'the nose of the camel under the tent', 'the slippery slope', and 'the wedge', are frequently found in the literature dealing with the ethics and morality of selective abortion and related matters. They are convenient ways of directing attention to wider social consequences which may flow from this innovation in medical practice, and to further innovations which may come to be tolerated once this innovation has become generally accepted as the norm.

Most of these possible consequential developments are seen as socially undesirable and morally unacceptable by contemporary ethical standards. But their appearance is likely to be insidious, so although such consequences may not be in the minds of those who advocate the present innovation, they may come to occur before people have noticed what is happening. Consequently, attempted predictions of what may eventually follow from present practices, speculative though they may be, are regarded as a valuable line of argument either because they will help to prevent the insidious appearance of undesirable consequences by making people aware of the possibilities and so arm them for resistance if they should occur and before the process has gone too far; or because if the undesirable consequences are seen as inevitable then the present innovation can itself be resisted.

An instructive illustration of the insidious way consequences can flow from an apparently modest and morally acceptable innovation and yet eventually result in what is in effect a complete reversal of moral standards has been cited by Sissela Bok (8):

John Cadoux, in *The Early Christian Attitude to War* offers an example of such a development (9). He describes the strong revulsion felt by the early Christians to war and to violence. There is no reliable evidence of the existence of a single Christian solder until after 170 A.D., and no Christian author undertook to show that Christians might be soldiers, in the first centuries A.D. But slowly, some soldiers came to be baptized, and were allowed to remain in the army. If a Christian who was a soldier before conversion was allowed to remain one, it was argued, then it followed that a Christian layman might become a soldier if he wished to. If a few soldiers could be tolerated in the Church, then any number could be; if a few Christians could enlist, then any number could do so. Once the beginning had been allowed to pass, the obstacles in the way of a general reversion to the original standard became virtually insuperable. Christian wars came to be one of the most flagrant instances of the inability, even on the part of an organization founded on love and non-violence, to hold the line against the institutionalization of violence towards other human beings.

So with this illustration in mind it seems worth giving some thought to the possible future consequences which might ensue as the camel's nose of selective abortion progressively protrudes into the tent.

Selective abortion and selective infanticide

It has been pointed out, notably by the ethicist Paul Ramsey (10), that exactly the same arguments which are used to justify the deliberate elimination of abnormal foetuses identified by prenatal diagnosis, could also be used to justify the deliberate elimination of infants with the same abnormality who for one reason or another had not been identified prenatally. This puts most advocates of selective abortion in something of a logical dilemma, because while they feel that the abortion of a foetus with, say, Tay-Sachs's disease or mongolism is morally justified, they would as a rule regard deliberate infanticide for these conditions as morally repugnant.

It is true that there may be an element of ambiguity in this position, because many would not feel they were under a moral obligation to institute all the procedures of modern intensive care or surgery to save the life of such an infant, in the same way as

they might do for an infant who does not have a severe abnormality. However, few would regard it as morally acceptable to do away with such an infant deliberately, either by withdrawing ordinary care or giving some lethal drug.

Various conclusions can be drawn from this situation. Paul Ramsey (10) for example argues that since the same arguments used to justify selective abortion for say mongolism (for example, the undue hardship or misery which would come to a particular family), could equally well be applied to the question of infanticide for mongolism, then logically if infanticide of a mongol child is judged to be unacceptable so must also be its selective abortion in prenatal life.

He stipulates that 'as a formal matter, an argument for abortion must not also justify infanticide under the same conditions and for the same reasons'. And he applauds 'the cool logical analysis' of the geneticist J. V. Neel (11) to the effect that 'early abortion based on prenatal diagnosis can be viewed as the modern counterpart of infanticide based on congenital defect' as confirmation of his position, although this does not seem to be quite the way Neel saw it.

Other people of course do not go along with Ramsey in the ethical conclusions he draws from this 'camel's nose' argument. They might agree, though reluctantly, that there is a real ethical inconsistency and lack of logic in accepting the arguments for selective abortion but not for selective infanticide when applied to the same class of conditions. But they would prefer to be guided by such illogical ethics than allow considerations of pure logic to alter their attitudes to the two situations. After all there is much in modern social behaviour which if looked at at all closely, is quite illogical.

However, they are clearly on a 'slippery slope' and must consider how to resist the emergence of selective infanticide as the norm. One way which has been used to try and deal with the difficulty is in terms of the argument that by the time the foetus has become a newborn it has reached a state of independent existence and different ethical rules apply. But this is a difficult line of argument to sustain in logic because it is self evident that we are all dependent on others for our existence from foetal life to old age

and it is simply the degree of dependence and the physical manner in which it is maintained which varies. There are also differences in the degree of dependency from one individual to another and the mongol child, for example, is in general more dependent than other children.

In practice the line which is drawn between induced abortion and infanticide goes somewhere through the middle of pregnancy, legally at present at 28 weeks of gestation. This is taken to be the point when removal from intra-uterine existence without inevitable death becomes at least feasible. However modern methods of intensive care applied to premature infants are steadily pushing this point further back and it is perhaps gradually approaching the earliest period when prenatal diagnosis and selective abortion is practical for technical reasons. This may not in practice create much of an impasse. But there is something paradoxical about a situation in which a foetus may be judged at one point in time as a suitable candidate for abortion, and a very few weeks later, if prematurely born, as a candidate for the application of the powerful modern machinery of intensive care.

Whether or not we ever arrive at a point on the slope where selective infanticide is the accepted norm is hard to predict, and it seems likely that if it does arrive it would be a consequence of major social changes among which prenatal diagnosis and selective abortion would possibly have had only a minor role. Nevertheless it is salutary to be reminded that the justificatory arguments for the one are intrinsic in the arguments for the other.

Selective abortion and the living defective

A related though somewhat different set of undesirable social consequences which might possibly come about from the widespread application of selective abortion, has been particularly emphasized by the medical ethicist, Leon Kass. The slippery slope which he perceives is the progressive erosion of civilized attitudes towards individuals with genetically determined abnormalities. The general thrust of his argument is illustrated by the following extract (12):

The practice of abortion of the genetically defective will no doubt affect our view of and our behaviour toward those abnormals who

escape the net of detection and abortion. A child with Down's syndrome or with haemophilia or with muscular dystrophy born at a time when most of his (potential) fellow sufferers were destroyed prenatally is liable to be looked upon by the community as one unfit to be alive, as a second class (or even lower) human type. He may be seen as a person who need not have been, and who would not have been, if only someone had gotten to him in time.

The parents of such children are also likely to treat them differently, especially if the mother would have wished but failed to get an amniocentesis because of ignorance, poverty, or distance from the testing station, or if the prenatal diagnosis was in error. In such cases, parents are especially likely to resent the child. They may be disinclined to give it the care they might have before the advent of amniocentesis and genetic abortion. . . .

It may be argued that I am dealing with a problem which, even if it is real, will affect very few people. . . .

The point, however, should be generalized. How will we come to view and act toward the many 'abnormals' that will remain among us—the retarded, the crippled, the senile, the deformed and the true mutants—once we embark on a program to root out genetical abnormality? For it must be remembered that we shall always have abnormals—some who escape detection or whose disease is undetectable *in utero*, others as a result of new mutations, birth injuries, accidents, maltreatment or disease—who will require our care and protection. The existence of 'defectives' cannot be fully prevented. Is it not likely that our principle with respect to these people will change from 'We try harder' to 'Why accept the second best?' The idea of the 'unwanted because abnormal child' may become a self fulfilling prophecy, whose consequences may be worse than those of the abnormality itself.

This line of argument appears to lead Kass to a position where, while he would accept as socially tolerable the majority of abortions carried out for other reasons, he is dubious about the merits of selective abortions specifically intended to eliminate genetically abnormal foetuses. This is an unusual, if not unique, position and it is hardly likely to alter the views of those directly involved in selective abortion who see its merits precisely in the benefits it can obviously often confer in those particular families who can be identified as having a 'high risk' of a severely affected infant.

Kass, of course, is well aware of this, and his purpose in pressing the argument is perhaps more intended to try and make people

pause to consider how attitudes towards inborn defects might become altered in an undesirable way and to persuade them to give some thought to how such changes in attitude can be prevented. 'I am mindful', he writes, 'that my arguments will fall far from the middle of the stream, yet I hope that the oarsmen of the flagship will pause and row more slowly, while we all consider whither we are going.'

The threat of 'positive' eugenics

The danger of the acceptance of 'positive' eugenics as a public policy, has also been seen as something concealed behind the wall of the tent under which the camel's nose of selective abortion is protruding.

The eugenics movement, which can be said to have started with the ideas of Francis Galton towards the end of the nineteenth century, has had a long and on the whole inglorious history. Its general aim is to develop policies for the progressive improvement of the genetical composition of the human species in future generations. Nowadays it is customary to distinguish between 'negative' and 'positive' eugenic policies. Negative eugenic policies are aimed at preventing or limiting the birth of individuals with what are considered to be undesirable genes, so that these should become reduced in incidence in later generations. Positive eugenic policies are aimed directly at increasing the incidence of genes thought to result in desirable human qualities.

Selective abortion of genetically determined abnormalities may be seen as a form of 'negative' eugenics, because it tends to reduce the incidence of such abnormalities in the next generation. But in the case of genes which produce autosomal or X-linked recessive abnormalities, or in the case of chromosomal translocations which produce abnormality in the unbalanced state, an actual increase in the incidence of the abnormal gene or the translocated chromosome in subsequent generations may occur because of reproductive compensation (see pp. 50–51, 56). Such a consequence can at least in principle be regarded as dysgenic, rather than eugenic.

An attempt to root out such deleterious genes or translocated chromosomes altogether would require a more 'positive' policy. For example, in the case of the gene (or genes) determining cystic

fibrosis it would involve in European populations the selective elimination of the 4 per cent or so of foetuses who are heterozygous for the gene, and who could be expected for the most part to emerge as normal healthy infants. This would presumably be achieved by screening potential pairs of parents to see whether one or the other was heterozygous and then monitoring all their pregnancies in order to identify the 50 per cent of foetuses who are heterozygous and abort them. Such a programme, which requires the abortion of large numbers of otherwise healthy foetuses, mainly in families in which cystic fibrosis was unknown, is hardly likely to commend itself in practice. And of course each additional recessive disease for which the programme is instituted adds its own toll of healthy heterozygotes. The general approach is in fact reduced to absurdity when one takes into account the now generally accepted conclusion from population genetics, that all of us are probably heterozygous for at least one gene which in the homozygous state would produce a grossly abnormal condition. So all foetuses are heterozygous for something which in homozygotes would be deleterious, and would therefore, by an extension of the argument, become candidates for abortion.

But the 'camel's nose' argument about 'positive' eugenics is usually more concerned with the possibility that the widespread acceptance of selective abortion could lead, in turn, to the acceptance of other new ways of interfering with human reproduction by the progressive application of recent discoveries in cell and molecular biology (often called 'genetic engineering'). Various possible applications of such discoveries to man have been discussed (13) but the one which has perhaps commanded most attention is based on the concept of 'cloning'. The idea is that it could become possible to replace the nucleus of an ovum from one individual by the nucleus from a somatic cell of another by *in-vitro* manipulation. The ovum containing the transplanted nucleus could then be allowed to develop *in utero,* leading to the birth of an infant with the same genetic constitution as the donor of the transplanted nucleus. In effect the new individual and the donor would be analogous to identical (monozygotic) twins, though they would not be born at the same time. They might even be separated by one or more generations if the transplanted

nucleus was taken from tissue culture cells which in principle can be stored in a frozen state for long periods, or if serial nuclear transplantation from one individual produced in this way to another were carried out. So a series of individuals all having the same genetic constitutions, a so-called clone, could in principle be produced.

Cloning (14) has been most successfully achieved so far in experiments on frogs, where the transplanted nucleus was taken from cells of the early embryo. It has also been accomplished, though with more difficulty, using nuclei derived from tissue culture cells derived from tadpoles and even adult frogs. The production of clones by the same general technique in mammals such as rabbits or mice evidently presents much more serious technical problems and has not apparently been accomplished yet. But there seems to be no theoretical reason why these technical difficulties should not be overcome in mammals as they have been in amphibia, and if so the practical possibility of the application of cloning to man would not be far away.

Cloning of course would be an obvious tool for 'positive' eugenics, since it bypasses the uncertainties introduced by gene segregation and recombination in sexual reproduction so that, in principle, the genetic constitutions of any individuals thought to possess particularly desirable qualities could be perpetuated indefinitely, and the number of such individuals in a population could be regulated at will.

The question, of course, is exactly what sorts of individual it would be thought desirable to perpetuate and increase numerically, and who would make the necessary decisions. Probably the only answer is that no one is, or will ever be, competent to decide for humanity as a whole. As Paul Ramsey (15) has put it, 'Men ought not to play God before they learn to be men, and after they have learned to be men they will not play God'.

Some may be tempted by the thought that it might be a good thing to have a clone of Mozarts or Einsteins around, though it is by no means clear that the particular attributes for which the prototypes are so admired, would appear and flourish when the expression of the same genetic constitutions were developed under quite different social and environmental conditions.

The main threat of this new technology has, however, been seen as the possibility that it would enable totalitarian governments to 'clone' sets of military men, technocrats, bureaucrats, and so on, who could be used as instruments to maintain their power. This threat can hardly be dismissed as fanciful after the experience of the gas chambers and concentration camps of Nazi Germany, with the deliberate elimination of whole sections of the community who were regarded as undesirable for racial or other reasons. These policies were of course carried through with techniques which were much less sophisticated than the new biological techniques which are beginning to emerge and which are potentially available for the future. But the older techniques are still at hand, so resistance to such political policies of so-called racial improvement will still be needed even if the application of 'cloning' to man can be prevented.

CONCLUDING REMARKS

It is inevitable that any discussion of the ethics or morality of selective abortion for genetic abnormality should mainly concentrate on its possibly undesirable aspects. This is particularly so when considering the 'camel's nose' or 'slippery slope' type of argument where emphasis is placed on the long term undesirable consequences which might possibly ensue.

There is therefore a danger of forgetting or not giving proper emphasis to the real benefits that the procedure can confer. It is, for example, no mean achievement to be able to offer to parents who have already had a child with a severe autosomal recessive abnormality such as Tay-Sachs's disease, the opportunity of being certain that their next child will not suffer from this condition. Previously all they could have been told was that there was a 1 in 4 chance that any future child would have the same abnormality, and there was no other information available which could usefully help them to make up their minds as to what to do. Similarly, it is no small advance that a woman who happens to become pregnant over the age of 40, and who previously could only be told that there was a risk of about 1 chance in 60 that her infant would be a mongol, can now early in the pregnancy be offered in the

great majority of cases the certain information that the child will be chromosomally normal, and in the cases where this is not so has the opportunity of an abortion.

Such real and visible benefits make it appear certain that prenatal diagnosis and selective abortion will become more widely applied and that facilities for it will increasingly be made available. And this development is hardly likely to be much impeded by the kind of arguments and considerations which have been discussed above.

Questions about the degree of severity of conditions for which this approach is justified still remain to be resolved, and no doubt will be increasingly discussed and argued about as the potential scope of the procedure is widened. Similarly there are good reasons for continuing to appraise the possible long-term social consequences which might result as the practice becomes extended.

However, the benefits it can produce when applied with care and discrimination are now sufficiently clear, that there remains little doubt that it represents a valuable advance in medicine.

APPENDIX I

Incidence of gross chromosomal abnormalities in spontaneously aborted foetuses

The estimates in the table come from a review by D. H. Carr (1).

Gestational age	*Spontaneous abortions* (%)	*Percentage with chromosomal abnormalities in each age-group*	*Incidence of chromosomal abnormalities among all spontaneous abortions*
Up to 13 weeks	79·0	40	0·316
13–17 weeks	14·3	25	0·036
17–21 weeks	6·7	3	0·002
Total	100·0	—	0·354

Assuming that 15 per cent of foetuses are aborted spontaneously, the data suggest that 5·3 per cent of all foetuses have a chromosomal abnormality sufficiently severe as to result in spontaneous abortion.

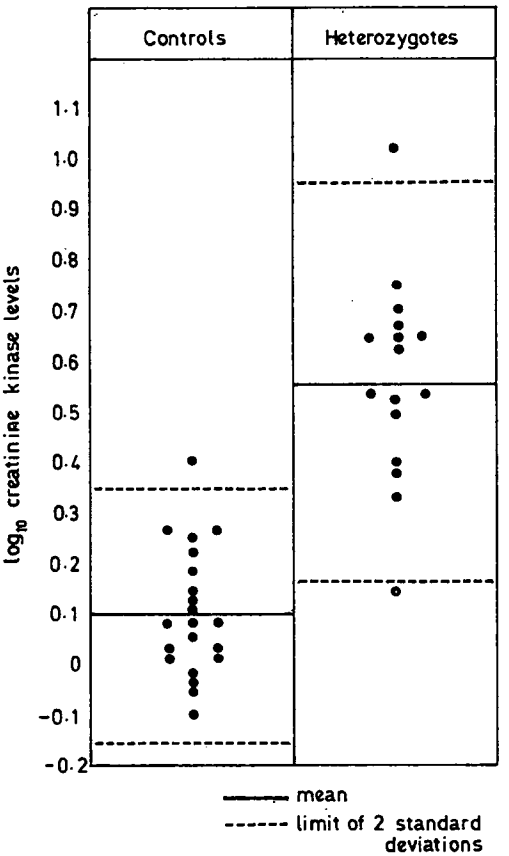
Among new-born infants (2) about 0·18 per cent have a phenotypically severe abnormality due to chromosomal aberration (ie autosomal trisomies, unbalanced translocations, deletions, and XO). Thus only about 3·3 per cent of all foetuses with at least this degree of chromosomal abnormality survive to term.

See references on p. 100.

APPENDIX 2

Detection of heterozygotes for the gene determining the Duchenne type of muscular dystrophy

The following data from the study of Wilson, Evans, and Carter (1), illustrate the degree of discrimination which may be achieved by serum creatine kinase determinations between heterozygotes for the



See reference on p. 100.

gene determining severe Duchenne muscular dystrophy and unrelated control subjects.

The comparison was made between 17 women known from family studies to be heterozygotes, and 21 controls (all adults). The level of creatine kinase activity taken for each subject was based on a mean of the enzyme assays on three separate serum samples collected on different days. This was to minimize the effects of daily variations.

The separate points in the distributions represent the activity level for each subject expressed in $\log_{10}$ units. The logarithmic transformation was found to be convenient because it provided a more nearly 'normal' distribution of the values in each group.

For the 21 control subjects, the mean creatine kinase activity level was (in $\log_{10}$ units) 0·102 with a standard deviation of 0·127. For the 17 heterozygotes the mean was 0·563 with a standard deviation of 0·194.

Comparison of the two distributions suggests that optimal discrimination between heterozygotes and normals is obtained by taking values above and below 0·283 ($\log_{10}$ units) which is 1·44 standard deviations from each of the two means. On this basis approximately 10 per cent of normal subjects would be misclassified as heterozygotes and vice versa.

APPENDIX 3

Some 'inborn errors of metabolism' in which prenatal diagnosis is possible by direct enzyme assays or related biochemical studies on amniotic fluid cells in tissue culture

[For detailed references see Milunsky (1), Stanbury, Wyngaarden, and Fredrickson (2).]

Disorder	*Deficient enzyme*
Tay Sachs's disease	N-acetyl hexosaminidase A
Sandhoff's disease	N-acetyl hexosaminidase A and B
Generalized gangliosidosis	GM_1-β-galactosidase
Gaucher's disease	glucosylceramidase
Krabbe's disease	galactosylceramidase
Ceramide lactoside lipidosis	ceramide lactoside-β-galactosidase
Metachromatic leucodystrophy	aryl-sulphatase A
Niemann-Pick disease	sphingomyelinase
Wolman's disease	'acid' lipase
Fucosidosis	α-fucosidase
Fabry's disease	α-galactosidase
Hurler syndrome	α-iduronidase
Hunter syndrome	sulphoiduronate sulphatase
Sanfilippo syndrome A	heparan sulphate sulphatase
Sanfilippo syndrome B	N-acetyl-α-glucosaminidase
Pompe's disease (glycogen storage disease type II)	α-1,4-glucosidase
Glycogen storage disease type III	amylo-1,6-glucosidase
Glycogen storage disease type IV	amylo-(1,4→1,6)-transglucosidase
Galactosaemia	galactose-1-phosphate uridyl transferase
Mannosidosis	α-mannosidase
'Acid' phosphatase deficiency	'acid' phosphatase
Lesch-Nyhan syndrome	hypoxanthine-guanine phosphoribosyl transferase

See references on p. 101.

Appendix 3

Disorder	*Deficient enzyme*
Oroticaciduria	orotidine-5′-phosphate pyrophosphorylase *and* decarboxylase
Maple syrup urine disease	'branched chain ketoacid decarboxylase(s)'
Argininosuccinic aciduria	argininosuccinase
Citrullinaemia	argininosuccinic acid synthetase
Homocystinuria	cystathionine synthetase

APPENDIX 4

Galactose-1-phosphate uridyl transferase activity in different genotypes

The table shows the approximate relative activities of galactose-1-phosphate uridyl transferase in individuals of different genotypes.

Three different alleles are considered; Gt^N is the so-called normal allele; Gt^D is the allele which in homozygotes results in the Duarte variant (1) and Gt^G is the allele which in homozygotes results in galactosaemia.

The activities given for each genotype represent mean values. There is, however, considerable variation of activity within each genotype, the standard deviations being about 10–20 per cent of the mean in each case (2), and this results in various degrees of overlap between the distributions for different genotypes.

Genotype	*Relative activity of galactose-1-phosphate uridyl transferase (1)*	*Approximate population incidence* %	*Clinical abnormality*
Gt^N Gt^N	100	88·6	—
Gt^N Gt^D	75	10·4*	—
Gt^N Gt^G	50	0·7†	—
Gt^D Gt^D	50	0·3	—
Gt^D Gt^G	25	0·04‡	—
Gt^G Gt^G	0	0·0013†	galactosaemia

* Based on estimate of incidence of Gt^DGt^D derived from population surveys (1).

† Based on average of estimates of the incidence of galactosaemia among newborn obtained in various newborn screening programmes (3).

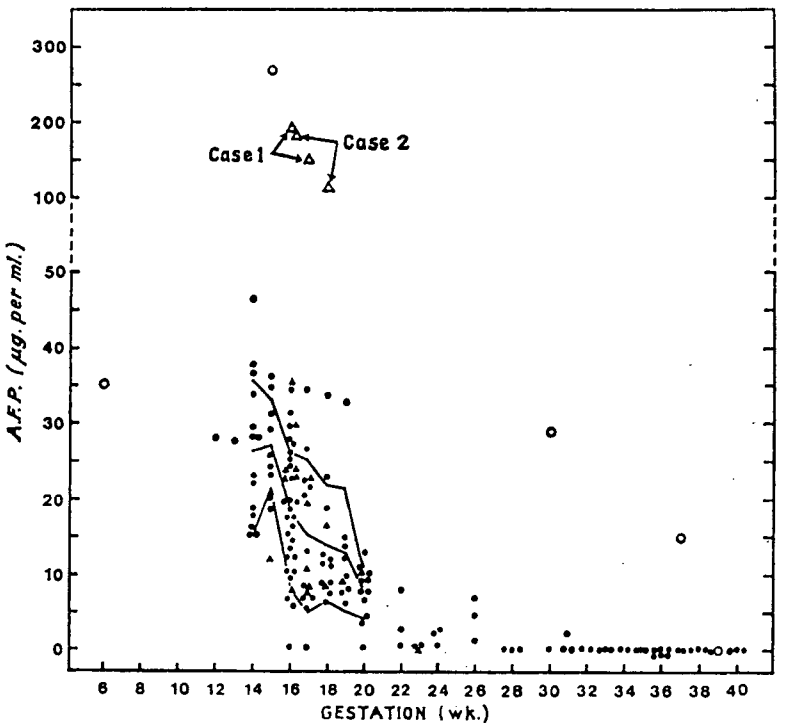
‡ Based on gene frequency estimates derived from * and † above.

See references on p. 101.

APPENDIX 5

Data illustrating the use of α-foetoprotein determinations in amniotic fluid for the prenatal diagnosis of neural tube defects

The diagram summarizes the study of Allan *et al.* (1).



Key

● Control series. The continuous lines indicate mean ± standard deviation at different gestational ages in a series of 140 pregnancies.

▲△ Prospective series of 20 pregnancies known to be at risk because of the previous birth of an infant with a neural tube defect. Cases 1 and 2 (△) were found to have high α-foetoprotein levels associated with neural tube defects.

○ Amniotic fluids studied retrospectively in 5 cases where a neural tube defect was known to have occurred.

See reference on p. 101.

APPENDIX 6

An approximate idea of the reduction in birth incidence of an autosomal recessive abnormality, produced by selective abortion of affected foetuses in pregnancies identified as being at risk because of the previous birth of an affected child, can be obtained by the following simple argument, due to Fraser (1).

Consider a series of couples both of whom are heterozygous, and suppose they each aim to have n children. Suppose that once an affected child is born all subsequent pregnancies are monitored with the selective abortion of affected foetuses until the total desired number of children (n) is reached.

The completed families can be divided into two groups:

(*a*) A proportion, $(\alpha)^n$, will have only normal children and no affected children. [This follows from the fact that the chance of any particular child being normal is α, so the chance that all n children will be normal is $(\alpha)^n$.]

(*b*) The remainder of the families $[1-(\alpha)^n]$ will each have one affected child and $[n-1]$ normal children.

So the mean number of affected children per family is:

$$1-(\alpha)^n.$$

If, however, there was no selective abortion the mean number of affected children born per family would be $n/4$.

So the proportionate reduction in the incidence of the condition at birth will be:

$$\frac{n/4-[1-(\alpha)^n]}{n/4}.$$

The proportionate reduction in birth incidence varies according to the value of n, as shown in the table.

The total effect will of course depend on the distribution of family sizes. If, for example, families of sizes 0, 1, 2, and 3 are represented in the proportions 1 : 1 : 5 : 3, the mean number of offspring per family would be 2, and the proportionate decrease in birth incidence of the abnormality would be about 17 per cent.

See reference on p. 101.

Appendix 6

n	*Proportionate decrease in birth incidence*	$=$	$\frac{\frac{n}{4} - [1 - (\alpha)^n]}{\frac{n}{4}}$
1		0	
2		0·13	
3		0·23	
4		0·32	
5		0·39	
6		0·45	

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