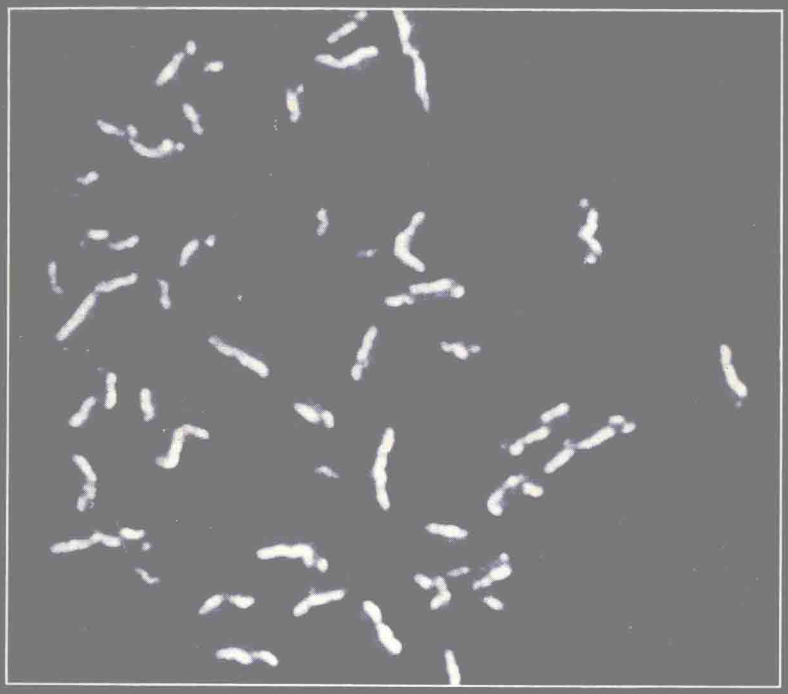

PRENATAL DIAGNOSIS AND SELECTIVE ABORTION

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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