Papers and Originals

Some Practical Applications of Genetics in Medicine and Surgery*

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Brit. med. J., 1964, 2, 1217-1221

Leonard Parsons was a man of transcendent ability and of transcendent personality. He was a pioneer in the study of child health and in the care of sick children. His memorial may be seen in the school of paediatrics which he founded in the University of Birmingham, and also in many other centres in this country and all over the world where his disciples have followed his example and practised what he taught. I could not hope to add to the tributes which have been paid to him, but I should like to mention one example of his insight and of his wisdom which comes close to the subject of these lectures. In 1933 he put forward the hypothesis that icterus gravis, hydrops foetalis, and haemolytic anaemia of the newborn were one and the same disease, due to a haemolytic process of then unknown nature. This conception prepared the way a few years later for the brilliant work of Levine. Levine showed that the haemolytic process was the result of maternal-foetal incompatibility. It is interesting to reflect that if the work on the rhesus monkey had been carried out a year or two later, or indeed if it had never been done at all, all we know now would probably have stemmed just as surely from Levine's observations, and without any help from our small relative. That was an example of Parsons's insight. About 12 years later he also showed his wisdom. In the early flush of enthusiasm it was proposed that haemolytic disease should be called rhesus disease. This Parsons opposed strongly, and thanks to him we now refer to haemolytic disease of the foetus and of the newborn. He was, of course, entirely right. To-day we know that although the commonest cause of haemolytic disease is maternal-foetal rhesus incompatibility there are many other causes as well, such as other blood-group antigens—for example, the original antigen of the Kell system.

Change in Relative Importance

It was natural for the early paediatricians, and indeed even for those of Parsons's day, to concentrate on the environmental causes of diseases of children. The scope for prevention was still enormous; but as environmental causes were progressively elucidated and appropriate measures of prevention and treatment instituted a hard core of something resistant assumed an ever-growing relative importance. In the quinquennium 1901-5 the infant death rate was about 140 per thousand. By a smooth progression this has fallen to about 20 per thousand. Nearly all causes of death have shown a substantial or indeed striking decline, but there are two exceptions. One is deaths attributed to injury at birth, a subject outside the scope of these lectures. The other is deaths attributed to congenital malforma-

tions. The infant death rate due to this last cause has not varied appreciably during 60 years; it has remained steady at about 5-6 per thousand. The consequence is that while in 1900 congenital malformation was responsible for only about one infant death in 32 it now causes nearly one death in four.

The change in more clearly genetic terms is shown by some figures analysed by Carter (1956), taken from the records of Great Ormond Street Hospital of children coming to post-mortem examination. Two years were singled out for comparison, 1914 and 1954. In 1914 environmentally determined conditions accounted for two-thirds of all deaths, the main causes being tuberculosis, pneumonias, and intestinal infections. By 1954 the proportion had fallen to one-seventh, the balance including genetic and partly genetic causes, and diseases of unknown origin. The conditions classified as of unknown origin included some congenital malformations and the cancers of childhood. The partly genetic group included such conditions as congenital pyloric stenosis and spina bifida.

The achievement has been great; there are now fewer fields to conquer, and it seems right to devote more attention to the hard core of genetic and partly genetic disease, and to those causes of child suffering and child mortality whose causation still remains mysterious.

Genetic Principles in Medicine

In general biology genetics is of central interest. It is also one of the essential disciplines in studying the causation of disease. But it is not of these fundamental aspects of the place of genetics in biology and medicine that I propose to talk in these lectures. The question I thought I should ask is *what* practical contributions genetics can make here and now, or in the reasonably foreseeable near future, to the practice of medicine and surgery. There are a number of these practical applications, some reasonably important, some making a modest contribution only, but adding up in total to something useful. But I should like to mention at the outset that in my view the most important single contribution is the provision of genetic advice for those who need it, a subject to be mentioned later. But there are a number of others.

Before considering the applications, however, a few basic principles might be recalled, however briefly. Inherited conditions depend on the presence of genes, and their transmission is governed by the behaviour of the chromosomes which bear the genes. Thus with a dominant gene we get direct transmission from parent to child. Affected persons married to normals have on the average children half of whom are affected and half normal. With defects due to recessive genes the pattern of transmission is entirely different. Two outwardly normal carriers happen to marry and then there is one chance in four that any child will receive the abnormal gene from both parents and so be affected. The characteristic finding is a tendency

* A shortened version of the Leonard Parsons Lectures delivered at the University of Birmingham on 13 and 14 May 1963.

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for such a condition to occur in more than one member of a sibship of brothers and sisters, and usually no other affected relative can be found. This is the pattern seen in fibrocystic disease of the pancreas, in galactosaemia, in phenylketonuria, in Werdnig-Hoffmann's disease, and in many more. Sometimes, however, genes are neither dominant nor recessive. One dose of the abnormal gene does a certain amount of damage; two do more. This is what is found with sickling and sickle-cell anaemia, and with thalassaemia minor and full-blown Cooley's anaemia. It should be added that with improved laboratory methods it is becoming increasingly possible with a number of genes formerly considered recessive to detect the carriers, though usually there is an overlapping of normal values.

Then there are the sex-linked abnormalities. These are important in man, for they are numerous and include such conditions as haemophilia, Christmas disease, the Duchenne type of muscular dystrophy, and red-green colour-blindness. Most sex-linked genes are recessive, so what is observed is transmission to half the sons of outwardly normal carrier women; on the average half the daughters of these women are in turn carriers. An affected man cannot transmit to a son, but all his daughters will be carriers.

In addition to the simply inherited defects there are many conditions which are partly genetic. Inheritance is no longer simple, but there is an increased incidence in relatives. Mendelian ratios cannot be fitted, but if large-scale studies are carried out useful empirical figures can be obtained for the risk to relatives of various kinds. Sometimes the underlying basis may be a gene which is not always expressed; but more often, in all probability, the genetic element is multifactorial—that is, it depends on the combined action of many genes, of small effect individually, but additive in their action.

Early Diagnosis

The first practical application I should like to consider is how genetics can sometimes facilitate early diagnosis, particularly when early recognition and early treatment are important. One very good example, involving a dominant gene, is multiple polyposis of the colon and rectum (Dukes, 1952). This is of course a precancerous condition, and early diagnosis, with appropriate surgery, has saved many lives—and will save many more provided those at risk can be examined at an early age for the presence of polyposis. Dr. Dukes is now in touch with many families, some of them very large.

Galactosaemia (Schwarz, Wells, Holzel, and Komrower, 1961) is a condition that is sometimes not easily diagnosed, and the consequences are then disastrous. In severe cases, about a week after birth, there occur listlessness, refusal to feed, and vomiting, followed by loss of weight, liver enlargement, jaundice, and diarrhoea. There are signs of gross liver damage, haemorrhages, ascites, and oedema. Early death is the rule. In some cases the effects are less severe, but cirrhosis of the liver, cataracts, and mental deficiency are common. The metabolic defect is a deficiency or abnormality of the enzyme galactose 1-phosphate uridyl transferase and the body is unable to metabolize galactose. If lactose is excluded from the diet practically normal physical and mental development can be ensured. As with so many of the inborn errors of metabolism, a recessive gene is responsible. Following the birth, and perhaps the death, of an affected child, it is known that the risk is one in four that any subsequent child will be similarly affected, so that all concerned can be ready to recognize the condition at the earliest moment and start the relatively simple but life-saving treatment.

Phenylketonuria provides another example. It is due to a recessive gene. There is a failure to metabolize phenylalanine, and the consequences in the absence of treatment are nearly always extremely bad, the worst being mental deficiency, usually

of profound degree. A diet very low in phenylalanine can, however, secure much more normal development. The results are promising, and it may be that relatively normal physical and mental development can be ensured provided that treatment is started early enough. As with galactosaemia, the birth of an affected child warns all concerned that the risk is one in four for any subsequent child.

Nephrogenic diabetes insipidus is sex-linked. It is not an easy condition to diagnose, and, once again, if this is not done the effects are serious. There is usually severe mental impairment and early death is common. But provided a diagnosis is made early enough physical and mental development may be relatively normal. There is another and very great advantage. As shown by Carter and Simpkins (1956), the carrier women can always, or practically always, be identified by their failure to produce a normally concentrated urine. Hence, when a case has been diagnosed the female relatives can be tested, and it can be discovered which of them run the risk that any son has a 50% chance of having diabetes insipidus.

The examples I have mentioned so far are rarities, but it might be pointed out in passing that although the great majority of simply inherited abnormalities are rare they are not of negligible importance in the aggregate, because there are so many of them. But let us turn to something much commoner—namely, congenital pyloric stenosis, the commonest reason for surgical intervention in neonatal life. This is a condition with a frequency of about one in 200 male births and about one in 1,000 female births. The genetics are not simple, but there is a strong genetic element. Carter (1961) has shown that the empirical risk to relatives is high. Thus, sons or brothers of affected men have a chance of 7 to 8% or so of developing the condition. With the sons or brothers of affected women the risk is much higher, being no less than about 20%. Treatment is highly effective, and the cure lifelong, but it is very important to make an early diagnosis. Actually, during the course of the Great Ormond Street studies the investigation itself led to the diagnosis and successful treatment of two or three cases which had hitherto been missed.

Fibrocystic disease of the pancreas is the commonest simply inherited disease in our own population. Early diagnosis, based on family history, can facilitate the differential diagnosis and prompt surgical treatment of meconium ileus; and with those whose symptoms develop later the first signs of lung involvement can be treated at once with antibiotics.

The genetics of Hirschsprung's disease are by no means simple, but thanks to the work of Bodian and Carter (1963) we know that the risk to relatives of those with the long-segment variety of the condition is relatively high, being about one in seven for brothers of affected boys. Prompt operative treatment offers the best chance for survival, and I might mention a recent case in which, thanks to the family history, a diagnosis of long-segment Hirschsprung's disease was confirmed histologically within 18 hours of birth. Unfortunately, in this instance the child did not survive the operation, but at least the best chance had been afforded of saving a desperate case.

I have left to the last what promises to be one of the best examples of all. Miller and Paterson (1962) published a paper on heredity in glaucoma simplex. Four out of 50 sibs of affected persons were also affected, and two out of 75 children. But a measure of the coefficient of outflow from the anterior of the eye, the Friedenwald index, gave striking results. The upper limit of normality is taken as 100, and though some few of the sibs and children of control subjects just attained this value only one exceeded it. On the other hand, just about half the sibs and half the children of the subjects with glaucoma gave abnormal values. Furthermore, there was little change with age, abnormal values being apparent in the youngest subjects studied, down to the age of 15 years. These results strongly suggest a simple dominant gene whose presence can be detected by a measurement, though of course only a minority of those having the gene will actually develop glaucoma. If all

this works out, and it seems convincing, then relatives at risk can be identified, even at a relatively early age, and kept under observation. It might be worth doing, not only for sibs and children of people with glaucoma simplex, but for nephews, and perhaps even for first cousins, as well.

Family History in Common Diseases

So far I have been mainly concerned with simply inherited differences or with those in which the genetic element is proportionately very important. Even with pyloric stenosis, for example, which is not simply genetic, the incidences in relatives of different kinds vary from 10 times the general population frequency in male first-degree relatives of affected males to 80 times the population frequency in female first-degree relatives of affected females. With some of the simply inherited conditions the disproportion is of course far greater. The importance of such disproportions in helping with diagnosis needs no emphasis. But when we turn to the genetic element in common diseases the picture is very different. Even with diseases in which it is manifest that there is some genetic element the genetic contribution is usually relatively small. The usual sort of figure is that first-degree relatives may be, say, twice or three times more likely to develop the disease than random members of the general population. Now, no one will dispute the usefulness and importance of this knowledge in studies on the aetiology and epidemiology of the diseases concerned; but does it help very much in the diagnosis and management of the individual case? I must admit that I have considerable doubts. In fact, I would go so far as to say that with ordinary common diseases the family history tends to be overvalued, not undervalued, both by the doctor and by the patient, and this may be misleading and even harmful.

In the admirable survey of Doll and Buch (1950) on duodenal ulceration it was shown that the incidence of duodenal ulceration in the brothers of affected men was about 2.8 times expectation as against a comparable control sample matched for age. So what?—that is, in terms of the individual case? Is the physician or surgeon to be influenced in his judgment by knowing that a risk is twice as great as for the random person? There are many other factors that are more potent; for example, a woman is six times more likely than a man to develop a duodenal ulcer. There are often big geographical variations too.

Even an apparently striking concentration in a family group needs to be interpreted with caution if the condition is a common one. Here is an example. A man had died following a haematemesis or a perforation—I forget which. His wife had had a partial gastrectomy for peptic ulcer. Their one daughter was normal, but their son, aged 18, perforated while riding his bicycle and died in hospital. But is this more than coincidence? Personally, I should not be inclined to attach much weight to it unless it was part of a systematic large-scale survey, when it could be decided whether such happenings are unduly frequent and do indeed indicate a specially high risk in particular instances. Useful applications to individual cases can be made only against the background of such surveys, and I think we should often find ourselves able to dispel vague, or not so vague, fears in the minds of patients of the hereditary doom awaiting them.

Genetically Determined Drug Sensitivities

The number of known drug sensitivities having a genetic basis has grown rapidly during recent years. A striking instance is provided by the South African variety of porphyria, porphyria variegata (Dean and Barnes, 1955; Dean, 1963). It is determined by a dominant gene. It is estimated that there

are no fewer than about 8,000 bearers of the gene in the white and coloured populations of South Africa. In the Eastern Cape the population frequency reaches about 1 in 250. Thanks to painstaking researches, extending over many years, Dean has been able to show that all the affected persons are descended from a single couple who married in 1688, and there can be no doubt that a single mutation is responsible and that one or other of the original couple must have carried the gene. Under natural conditions no great harm results, as witnessed by the fantastic spread. There are often skin lesions and sensitivity of the skin to sunlight, and these may be troublesome. Some people, especially women, have acute episodes, with neurotic and psychotic symptoms. But there are often long periods of remission and some bearers of the gene may be symptom-free throughout life. Its presence can always be detected, however, at least in adults, by the presence of porphyrin in the stools.

It was the introduction of barbiturates, and, above all, of barbiturate anaesthetics, that transformed the situation. Barbiturates are apt to induce acute attacks, which often end in total paralysis and death. Many fatalities have been reported. At some South African hospitals it is now routine to test for porphyrin in the stools before administering a general anaesthetic. Many affected persons have been given cards warning doctors that the dangerous drugs must not be administered.

Pseudocholinesterase deficiency came to light thanks to the work of Lehmann and Ryan (1956). Under natural conditions this enzyme defect does no apparent harm—at least, none has been discovered so far. But if suxamethonium is used as a muscle relaxant during anaesthesia there may be a prolonged and dangerous apnoea. At first it was thought that a simple recessive gene was responsible, though from the beginning it was realized that the gene was not completely recessive, as many heterozygotes have a lesser degree of the enzyme deficiency. It is now known that the genetics of this condition are more complicated. There are several abnormal genes, which may form a series of multiple alleles. It is estimated that about one person in 2,000 in our population is suxamethonium-sensitive.

Then there is the sex-linked gene which produces the condition originally known as primaquine sensitivity. It is an extremely common gene in certain populations. Among American negroes about 14% of men are hemizygous and affected, the proportion of homozygous affected women being, as it should be, about 2%. In some parts of the world the gene frequency reaches extraordinarily high figures. For example, it is about 60% in Yemenite Jews in Israel. As of course is inevitable, under natural conditions the gene causes little or no harm, apart from the eating of fava beans. But a wide range of drugs—for example, the sulphonamides—may induce a haemolytic anaemia. Again, it is an enzyme deficiency, this time of glucose-6-phosphate dehydrogenase. As with sickling and thalassaemia, there must be a reason why an abnormal gene should have become so frequent in some parts of the world. There is, in fact, good evidence that, as with them, it is a matter of greater resistance to malaria.

There are other ramifications too. Variations in response to drugs may increasingly be found to have a genetic basis. Thus it is known that human beings fall into two groups—those who are fast inactivators of isoniazid and those who are slow inactivators. It seems to be a simply determined genetic difference, slow inactivation being recessive (Evans, Manley, and McKusick, 1960). There are interesting racial differences in frequency. In Caucasians, negroes, and Indians the frequencies of the phenotypes are about equal, whereas in Japanese and Eskimos more than 90% of the population are fast inactivators. It is not yet clear whether the efficiency of treatment of pulmonary tuberculosis with the drug differs in the two types of person, though it may well prove to be so. There is no association with the development of drug-resistant strains of the bacillus; but it has been shown that slow inactivators are more likely to develop peripheral neuritis as a result of treatment.

Chromosome Abnormalities

Efficient techniques for the examination of human chromosomes were not available till 1956, and it was impossible to detect even gross aberrations. I remember talking to a very eminent cytologist some years ago. He said that he thought it probable, though of course he could only guess, that the loss of a complete chromosome, or duplication of a complete chromosome, in a mammal would be lethal. The truth proved to be far different, and from the beginning of 1959 we have seen the discovery of a large array of abnormalities, involving whole chromosomes and also parts of chromosomes.

Plant and animal cytologists are very aware, of course, that the human chromosome anomalies are nothing new to them. Similar examples have been known for 20, 30, and even 50 years; but, I would add, not until very recently, and not until the human examples came to light, in mammals. Here I should like to be historical for a moment. Non-disjunction of the chromosomes was first observed by Gates in 1908. But the immense volume of work which grew up afterwards was due to Bridges, the American geneticist. It was one of the most important landmarks in the whole history of genetics. Abnormal genetic ratios had been observed in *Drosophila*, and these seemed to threaten the entire basis of the chromosome theory of heredity. Bridges worked on, and then in 1916 published a paper with the triumphant title "Non-disjunction as Proof of the Chromosome Theory of Heredity." The cytological observations and the genetic findings tallied perfectly, and it was indeed this work which carried, at last, almost universal conviction that the genes were borne by the chromosomes.

The discovery of the exactly similar phenomenon in man dates from 1959. Owing to non-disjunction of sex chromosomes individuals are found with two X's and a Y; more rarely the constitution may be XXXY or XXXXY. These individuals suffer from Klinefelter's syndrome. The loss of a sex chromosome gives a person with one X only, who suffers from Turner's syndrome. Triple- and quadruple-X females are relatively common and usually show little abnormality. With chromosomes other than the sex chromosomes, the autosomes, the presence of chromosome 21, one of the smallest human chromosomes, in triplicate instead of duplicate, determines Down's syndrome (mongolism). Trisomy of other autosomes produces two other syndromes—Edwards's syndrome and Patau's syndrome; the affected children are grossly abnormal and usually do not survive long.

Another important chromosome abnormality is translocation, whereby chromosomes of different pairs exchange segments. In a small proportion of cases of Down's syndrome the extra chromosome 21 is stuck to the end of another chromosome. The distinction is an important one, for with translocation mongols there may be a high risk of repetition through the reproduction of outwardly normal carriers of the translocation chromosome.

Thus in the study of intersex states, in Down's syndrome, and in some other congenital abnormalities chromosome studies are becoming increasingly necessary as a practical routine procedure.

Prevention of the Marriage of Carriers

With diseases due to what are ordinarily considered recessive genes, or to intermediate genes, it is possible to prevent the birth of affected children provided that the carriers can be identified and warned of the danger of marrying each other. At the moment this is a practical proposition only in those areas where there are common genetic diseases due to genes of high frequency. A good beginning has been made in those parts of Italy where the thalassaemia gene is very common. In the district of Ferrara about one person in 10 carries the gene, and

in some townships in that district one person in five (Bianco, Montalenti, Silvestroni, and Siniscalco, 1952). In those townships, given random mating, one child in every 100 suffers from Cooley's anaemia. A large-scale organization has been set up for testing the population, particularly schoolchildren. The carriers of the gene, who suffer from thalassaemia minor, can be identified. Registers are available and the carriers are made aware of the one-in-four risk of a child with Cooley's anaemia should they marry each other. Sickling is even commoner in parts of Africa north of the Zambezi, and doubtless when other more urgent problems of public health have been tackled a similar system will be instituted, and may lead to a notable reduction in the incidence of sickle-cell anaemia.

Whether anything of the kind will be done in communities where there is no very common harmful gene is something that the future will show. If fibrocystic disease of the pancreas is always due to the same gene, and there is some evidence pointing that way, about 1 in 20 of the English population carry it. If there were a test for detecting heterozygotes—and it may well come—it might perhaps be practicable to do something on the lines of the control of thalassaemia in parts of Italy.

Some Other Contributions

Some other applications may be mentioned in briefest summary. There are the mutagenic effects of ionizing radiations, with the implications they carry for future human welfare. Improved techniques and improved apparatus and the avoidance of unnecessary exposure in medical and industrial practice can limit the risk of genetic damage due to induced mutation. Then there is the whole story of haemolytic disease of the foetus and newborn, and the vast business of blood transfusion. There are the medico-legal applications of serology in cases of disputed paternity or suspected interchange of babies. In fact, much of the work of serologists is a study in the application of genetics, a study that has reached great refinement.

Genetic Prognosis

When all other applications have been considered, however, the most important single application, in my opinion, is the provision of genetic advice for those who need it. I will deal with this subject rather briefly, however, because I have referred to it in a fairly recent paper (Roberts, 1962).

The first question is: Who needs genetic advice? Experience at a genetic clinic shows that 90% of inquiries come from couples who have had a child suffering from some condition which may be hereditary, or with which there may be a chance of recurrence, and who want to know the risks should they have a subsequent child. I think this is as it should be. Before marriage it is only a very few couples who have anything in the family history which might make the seeking of advice advisable. I am not in favour of routine premarital genetic counselling. Apart from the great waste of time involved it would tend to encourage the neurotic. In the present state of knowledge, unfortunately, the need for genetic advice nearly always arises after the initial disaster has happened.

It is difficult to estimate numbers, but perhaps one might guess that, say, very roughly one person in 20 or so might really need genetic advice at some time during his or her life. As queries usually refer to couples, this is more like 1 in 40 in terms of queries.

Not many people really need genetic advice, but those who do need it need it badly. The decision whether or not to have further children may be a difficult one, and deep-seated emotions are involved. It is surely the duty of the doctor to provide information on risks of recurrence to the extent that knowledge permits, and that is to a very considerable extent. It is not a matter of doctor's advice or nothing. Couples will

in any event get plenty from other and very ill-informed sources, for the whole subject bristles with superstitions of the most useless kind.

The giving of genetic advice is facilitated by a great advantage, or rather by two advantages. The first is that bad risks are nearly always associated with simple genetics, when the observer knows just where he is. As the genetics become progressively more obscure, so, in general, do the empirical chances of recurrence improve. The second advantage is that risks tend strongly to separate themselves into two groups, the good and the bad. We may take bad risks as being those which are worse than 1 in 10; often, of course, they are considerably worse. Good risks may be taken as better than 1 in 20; often, of course, they are much better. Only very rarely does an estimate fall between 1 in 10 and 1 in 20. In assessing what I have called good risks we must always bear in mind that the risk that any random pregnancy will end with some serious malformation or other, or that some serious error of development will manifest itself in early life, is at least 1 in 40.

Genetic prognosis depends on three things. First, there is diagnosis. This may be obvious enough, but often is not. Furthermore, subclassifications may be important genetically. The second factor is the individual family history. This needs to be taken systematically. Close relatives are much the most important, and complete particulars should be noted, including such things as sex and age, and, of course, specifying normals as well as abnormals. The third factor is the background of the literature. This is the main reason why the genetic clinic is likely to be needed for some time to come. Inherited and partly inherited conditions are so numerous and the literature so scattered that it is difficult even for the specialist, unless he has a particular interest in genetics, to keep abreast of the genetics of conditions within his own specialism. Moreover, the quality of the various contributions has often to be critically assessed. There are complications, too—for example, alternative modes of inheritance, or non-inheritance, of what seems to be a single disease entity.

Psychological factors are very important. Much can be done to dispel feelings of guilt and of being different from other people. Patients can often be induced to see that it is just bad luck, of the kind that might have happened to anybody. Reassurance about the chances in regard to marriage and children for the normal children is very important, and it can often properly be given. This applies to other normal relatives, too—for example, younger sibs of the parents.

In the paper already quoted (Roberts, 1962) an account was given of a follow-up of couples seen at a genetic clinic. It was striking that the attitude of the couples to the advice given was very clearly reflected in the action actually taken—that is, in the number of children subsequently born. With the few given a bad prognosis but who nevertheless decided to go ahead, and the relatively large number for whom the risk was small and who said that they were reassured, the average number of subsequent children was 1.2 per couple. Those who said they

were doubtful had had 0.4 child per couple. Those for whom the risk was bad and who thought they should not have further children, plus those who in spite of being given a good prognosis said at the follow-up that they had not been reassured, had had an average number of only 0.2 child per couple. One of the lessons of the follow-up is the difficulty of reassuring some couples even when the risk of abnormality in a subsequent child is small or very small. Only half these couples told us that they had in fact been fully reassured. It is probable that better results would be obtained if the couples were to be seen again after an interval and the problem talked over a second time.

Summary

Genetics can make some practical contributions to the medicine and surgery of to-day. There is the facilitating of early diagnosis when prompt treatment is important. A note of caution is struck, however, about the danger of overvaluing the family history in common diseases. There is the growing range of drug sensitivities having a genetic basis. Chromosome abnormalities are assuming a growing importance in a variety of intersex states and in a number of congenital defects, including Down's syndrome. The avoidance of genetic disease by making carriers aware of the danger of marrying each other has already made considerable progress in some parts of the world where some abnormal genes are frequent. There may ultimately be applications to genes which are rarer. The genetic effects of ionizing radiation, the management of haemolytic disease of the newborn, the whole business of blood transfusion, and medico-legal applications provide other examples. There can be little doubt, however, that the most important single application is the provision of genetic advice for those who need it. Useful advice can in fact be given in the great majority of instances.

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