MEDICAL PRACTICE

Scientific Basis of Clinical Practice

Genetic Counselling

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With the spread of medical knowledge there is an increasing desire among the public to see into the future, and the most usual request is for information about risks to subsequent children when one has already been born with an abnormality. Alternatively, when parents know of a skeleton in the family cupboard, they may ask about the chances of its turning up in their grandchildren—though frequently what they really want is medical support against a marriage they dislike on other grounds. Least commonly of all, individuals about to get married may seek advice about risks to future children, but couples who do this are often obsessional—most young people who have decided to get married pay no attention to what anybody says, and in general this is probably a healthy attitude.

Advice on genetic matters should always be tendered in terms of probability, never certainty, and in these days of football pools patients almost all understand odds. A helpful yardstick is that about one pregnancy in 30 will produce either a definite congenital malformation or a serious developmental abnormality which appears early in life.[1]

Fairly precise information can be given only in a few cases—that is, those which show clear-cut Mendelian inheritance—and this may necessitate the study of many pedigrees. When this is found, the risks to subsequent offspring are too high to be accepted by most people. Some examples follow.

Autosomal Dominant Inheritance

In a disorder controlled by an autosomal dominant gene (for example, most cases of facio-scapulo-humeral dystrophy and Huntington's chorea) the chance of any given offspring having the disease if one parent is affected is one in two, and the risk is similar for subsequent siblings. In diseases of late onset, however, we have to take into account the ages of the people concerned. For example, an apparently healthy man of 50 whose father had had Huntington's chorea might well inquire what the chances were of himself and his grown-up sons (who wanted to marry and have children) developing the disease. Since he had reached the age of 50 without getting it, the chances are clearly much better than 50% that he will remain free, and Emery[2] gives details of the calculations which show that the probability in this instance of his son being affected is only about 1 in 12.

Autosomal Recessive Inheritance

If a child is born with a recessive trait (for example, albinism or phenylketonuria) the risk of subsequent siblings being affected is 1 in 4. If there is known to be a recessive condition in a family, cousin marriage within that family is, of course, risky, since two relatives will be considerably more likely both to carry the gene than would two unrelated people. When this is not so, cousin marriages carry little added risk to the offspring.

There is interesting further information on phenylketonuria, and Clayton,[3] reviewing the whole subject, points out that hyperphenylalaninaemia can arise in a variety of ways, and some children with it can tolerate more phenylalanine in their diet than those with classical phenylketonuria. In fact, it is not known whether some children should really be treated with a low phenylalanine diet. Furthermore, some infants present all the biochemical features of phenylketonuria but require increasing amounts of phenylalanine to maintain a normal level in the blood. It is thought that this condition arises from an abnormality in the phenylaminase transaminating system.[4] These children grow out of the abnormality completely.

In the classical case there is no doubt that, provided the diet is begun early, intellectual deterioration can be prevented: the problems are what phenylalanine level to try to maintain and when to stop the diet. In a treated phenylketonuric woman it should be reintroduced *before* she becomes pregnant, since otherwise all her children may be subnormal, even though

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genotypically they are only carriers. Possibly children with other forms of hyperphenylalaninaemias are treated unnecessarily, but with more accurate diagnostic criteria this may be avoidable in future.

Sex (X)-Linked Inheritance

If the disease is due to a sex-linked recessive gene on the non-pairing part of the X chromosome (for example, most forms of haemophilia and the Duchenne type of dystrophy) then an affected man married to a normal woman will have all carrier daughters but all his sons will be unaffected. Of the daughters of a carrier female half will be normal and half carriers, and of her sons half will be affected and half normal. This is well known, but in a disease such as haemophilia, if there is no family history, it is very important not to give the rather bad prognosis for relatives until one has considered the possibility of a mutation. If this has occurred in the patient then none of his sisters would be carriers. It may be very difficult to decide the point, but inquiries about the disease in maternal uncles and great-uncles are important.

Counselling in Chromosomal Abnormalities

In most cases of chromosomal abnormality the risks to subsequent children are near normal since the cause of trisomy and non-disjunction is not known, though in Down's syndrome (mongolism) due to trisomy maternal age is a factor. Table I gives information about the risks of recurrence in this variety of the disease.

TABLE I—*Relation of Maternal Age to Trisomy 21*

Maternal Age	Risk of Occurrence	Risk of Recurrence
20-30	1:1500	1:500
30-35	1:750	1:250
35-40	1:600	1:200
40-45	1:300	1:100
45-up	1:60	1:20

Redding and Hirschhorn, by courtesy of the authors and the editor of the March of Dimes Original Article Series, Vol. IV, No. 4, 1968.

DOWN'S SYNDROME CAUSED BY A 14 OR 15/21 TRANSLOCATION

Less frequently, Down's syndrome is caused by a translocation between a number 14 or 15 and a number 21 chromosome. Figure 1 shows the method of inheritance of this type of mongolism. There is fusion of part of a chromosome 21 and part of a chromosome 14 or 15, but an individual carrying this abnormality will not be affected, because, even though he has an abnormal chromosome in the sense that he has parts of two stuck together, he still has no excess of chromosomal material. Those of his children, however, who receive his abnormal chromosome and *also* receive his normal 21 will be trisomic, because they will have received a normal chromosome 21 from their other parent.

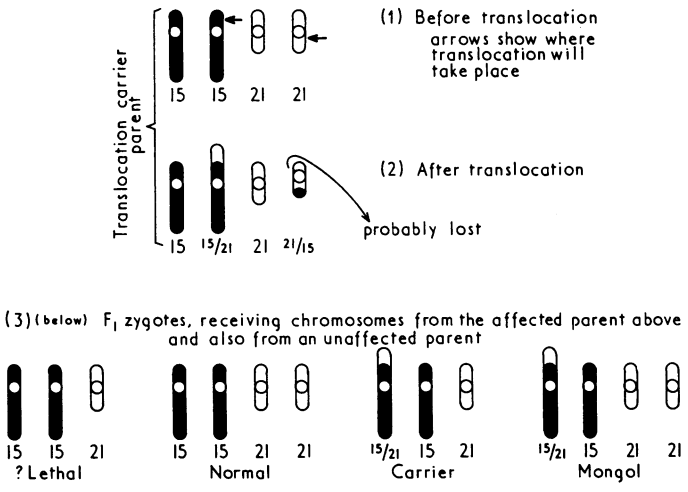

FIG. 1—Translocation as a cause of Down's syndrome. (By courtesy of Messrs Blackwell.)

This type of mongolism occurs in children of younger mothers, and it will be appreciated that it is not dependent on a chromosomal accident due in part to maternal age, but is brought about by the direct inheritance of an abnormal chromosome. Wherever there is a family history of mongolism in relatives, or where a young mother has already given birth to a mongol and is likely to have more children, it is well worth examining her chromosomes and those of her husband, and it would be very much the duty of a doctor to have such an investigation carried out. If a translocation is found in one of the parents there is theoretically an even chance of the child inheriting the translocation. If it inherits *both* the translocation *and* a chromosome 21 from its carrier parent, it will be a mongol because it has extra chromatin, the other 21 being derived from the normal parent. In fact, there is a less than 1 in 4 chance of producing a mongol, especially if the carrier parent is the father, since fewer abnormal gametes than expected are formed.

MULTIFACTORIAL INHERITANCE

This type of inheritance is, as the name implies, not dependent on one single gene (or pair of alleles) for which the individual is homozygous or heterozygous. It is not even dependent on genes only, but on the environment as well, and it means what it says—that is, that many factors are at work. The genes responsible will all be genes of varying but small effect, and with varying dominance, and it is not always easy to sort out which are the inherited components responsible for the condition and which the environmental ones. The term "polygenic" is nearly synonymous with "multifactorial" but differs in that it refers only to the genetic component of a character controlled by many genes.

It is easy to understand that characters which are controlled by many genes show continuous variation, whereas those which are controlled by single ones show clear-cut, either/or differences. It is quite simple to visualize the fact that many genes control human height—people are not "tall" or "short", they vary through all degrees of tallness and shortness with a few very tall and a few very short people at the two extremes. The vast majority of adults will fall in an intermediate group and if you draw a graph of their height you will obtain a "normal curve." There will be a sex difference and there will be racial differences, of course, and there will be the effect of nutrition, but the genes responsible for height are additive (as are those for intelligence). What is not nearly so easy, and gives rise to a great deal of very complicated mathematics, is the fact that diseases are very often multifactorily controlled. After all one either has or has not a disease—it is all very well to say that many genes add up to give you diabetes or a duodenal ulcer, but what constitutes the difference between "disease" and "no disease"? Here we come to the fact that there is a threshold beyond which the disease manifests itself—if you have enough genes predisposing to the disease, and also the environmental factors favour its expression, then you will have the disease. Here too there are sex differences, some diseases being more prevalent in one sex than in the other. Carter[5] has shown that in pyloric stenosis, which is commoner in boys than in girls, when a *girl* (that is, the wrong sex) has the disease she has more affected relatives than does a boy with the disease. The female baby is evidently normally more resistant to the disease than the male baby, and when she does develop it this is because she has a very high concentration of predisposing genes, and this is why more of her relatives will also have this high concentration of genes and show the disease.

The study of quantitative variation is of course statistical and the mathematics that are involved are not for the amateur, but Fraser Roberts[1] gives a very simple introduction to the principles, which are based on the resemblance between relatives. For each step farther away in relationship, the number of genes in common with one's relatives is halved. A parent passes on to a child half his or her chromosomes; they have half their genes in common. Clearly the child will pass on half the genes derived from that particular parent, so a grandparent and a grandchild will have a quarter of their genes in common, and so on. With a rare* dominant autosomal gene half the children of a person in whom it appears will receive it, a quarter of his grandchildren, and an eighth of his great-grandchildren. Half the parents and sibs of an affected person are therefore like the patient and half are unlike, and the likelihood of the other types of relative being affected can be calculated in a similar way. With multifactorial inheritance, however, many genes are combining together to produce the end result. On the *average*, half of the genes are making the sib or parent just like the subject, while half of them are making them no more like him than would be an unrelated subject. The difference is that instead of half the sibs or parents being totally like, and half totally unlike, all the parents and all the sibs are tending to be half-like. All the uncles and aunts are tending to be one-quarter-like; all the cousins one-eighth-like. These measures of resemblance are termed *regressions*, and multifactorial inheritance would follow the pattern indicated if there were no dominance and all the genes were intermediate in effect. This, of course, they are not, so dominance and recessiveness have to be considered and this involves complications. One effect of dominance in multifactorial inheritance, however, remains the same even though there are variations in dominance from gene pair to gene pair, and differences in the amount of effect produced by different genes: *the reduction of the regression for sibs is always half the reduction for parents* (meaning, as will be realized, that sibs are more like the subject than are parents).

The matter is a complicated one, but the above remarks will give the reader an idea of the arguments involved.

DETECTION OF CARRIERS

Another important aspect of counselling is the detection of carriers in genetic conditions. So far as the autosomes are concerned there are only two (thalassaemia and fibrocystic disease) which are fairly common. In thalassaemia (frequency as high as 5 to 15% in some parts of Italy and in Thailand) the saline osmotic fragility of the red blood cells is invariably reduced in the heterozygotes, and this is the best screening test for detecting carriers. In cystic fibrosis of the pancreas (frequency about one in 2,000 live births) a test for heterozygotes is in process of being worked out. Spock and his colleagues[6] found that affected individuals and carriers of fibrocystic disease possess an abnormal globulin which interferes with the normal rhythm of the cilia on the respiratory tract tissue of rabbits, and present investigations are concerned with a similar type of experiment.

In phenylketonuria a phenylalanine tolerance test will uncover a large proportion of heterozygotes and is also of great use in suspected homozygotes.

The detection of the carrier state is of much more importance in the commoner X-linked conditions (for example, in counselling the sister of a man with haemophilia), and in general the assessments are made by biochemical methods. Table II lists some of the diseases for which tests are available.

TABLE II—*Carrier Detection in X-linked Disorders*

Disorder	Abnormality
Haemophilia A	Factor VIII reduced
Haemophilia B	Factor IX reduced
G-6-PD deficiency	Erythrocyte Glucose-6-phosphate dehydrogenase reduced
Congenital agammaglobulinaemia	*In vitro* immunoglobulin synthesis by lymphocytes reduced
Lesch-Nyhan syndrome†	Hypoxanthine-guanine phosphoribosyl transferase in skin fibroblasts reduced. Two populations of cells
Hunter's syndrome	Granules in skin fibroblasts
Ocular albinism	Patchy depigmentation of retina and iris
Vitamin-D resistant rickets (hypophosphataemia)	Serum phosphorus reduced
Duchenne muscular dystrophy	Serum creatine kinase raised
Becker muscular dystrophy	Serum creatine kinase raised
Diabetes insipidus (nephrogenic)	Urine concentration diminished
Fabry's disease (angiokeratoma)	Urine glycolipids (ceramide hexosides) increased

(By courtesy of A. E. H. Emery[2] and E. & S. Livingstone)

†The affected boys, who lack the enzymes hypoxanthine and guanine phosphoribosyl transferase, show choreoathetosis and a behavioural disorder in which they tend to chew their own fingers and lips. They excrete enormous amounts of uric acid and eventually die with gouty renal disease.

AMNIOCENTESIS

Amniocentesis may now be used for genetic counselling in certain instances, always remembering that the technique is not without risk. A small quantity (2-5 ml) of amniotic fluid, which consists largely of fetal urine and contains cells from the fetal skin and amnion, can be removed, preferably about the 12th week of gestation. The cells can be sexed by observing the presence or absence of a Barr body, and grown in tissue culture, both to determine the karyotype and also to study biochemical abnormalities at a time when selective abortion may be desirable.

*If it were not rare, it might come in from both sides of the family and the model would not apply.

EMPIRICAL RISKS OF A FURTHER ABNORMAL CHILD

This is one of the most usual questions asked and is often difficult to answer (apart from the Mendelian cases already mentioned) since so many conditions are not inherited in a clear-cut way. This may be because: (1) the disorder is controlled by many genes (multifactorial inheritance); (2) the environment is also partly responsible; and (3) there is heterogeneity with differing aetiologies in the various sub-groups of the disease. In such situations the risks are empirical, the definition of this term being "the probability of occurrence of a specified event based upon prior experience and observation rather than on prediction by a general theory."[7] Table III gives the empirical risk figures for some common conditions which are not inherited in any simple manner.

TABLE III—*Empiric Risks for Some Common Disorders* (%)

Disorder	Incidence	Sex ratio M: F	Normal parents having a second affected child	Affected parent having an affected child	Affected parent having a second affected child
Anencephaly	0·20	1:2	2	—	—
Cleft palate only	0·04	2:3	2	7	15
Cleft lip ± cleft palate	0·10	3:2	4	4	12
Club foot	0·10	2:1	3	3	10
Cong. heart disease (all types)	0·60	—	1-4	1-4	—
Diabetes mellitus (early onset)	0·10	1:1	3	3	10
Dislocation of hip	0·07	1:6	4	4	10
Epilepsy ("idiopathic")	0·50	1:1	5	5	10
Hirschprung's disease	0·02	4:1			
male index			2	—	—
female index			8	—	—
Manic-depressive psychoses	0·40	2:3	10-15	10-15	—
Mental retardation ("idiopathic")	0·30 0·50	1:1	3-5	—	—
Pyloric stenosis	0·30	5:1			
male index			2	4	13
female index			10	17	38
Schizophrenia	1·00	1:1	14	16	—
Scoliosis (idiopathic, adolescent)	0·22	1:6	7	5	—
Spina bifida	0·30	2:3	4	—	—

(By courtesy of A. E. H. Emery[2] and E. & S. Livingstone)

Research Projects

STUDIES IN IDENTICAL TWINS

In any counselling unit twins are likely to appear and their research value lies in the fact that they may be discordant for a particular disease. A detailed history may then suggest why this is so. Identical twins discordant for Parkinsonism, for bronchial asthma, for chronic myeloid leukaemia, and for carcinoma of the breast (where both twins had Klinefelter's syndrome) have been recently encountered in the Nuffield Unit of Medical Genetics.

HYBRID CELLS

It has long been known that some virus infections of animals and man produce lesions in which cells with two or more nuclei are frequently found, and it is now known that this is due to the ability of the virus to fuse single cells together. The virus may be used to fuse different cell types from one species of animal, or cells from different ones. The hybrid cells combine the properties of the two parents, and have, to begin with, a double set of chromosomes. The technique has been used for studying linkage (a cell lacking an enzyme being fused with a cell possessing it) and it has also recently been applied to the study of cancer. Professor Harry Harris at Oxford[8] has fused highly malignant mouse tumour cells with non-malignant mouse cells, and then transplanted the hybrid cells into mice which had been irradiated to prevent them from rejecting the transplant (irradiation inactivates the immune response). Instead of a tumour forming in all the mice, which is what happens when the malignant cells alone are injected, tumours developed in *only a third* of them—that is, cancer did not occur as long as the hybrid cells retained the full double set of chromosomes (one whole set from each parent). When, after dividing, they gradually started to lose chromosomes, the hybrid cells began to become malignant again. Selective chromosome loss may, therefore, be a factor in causing cells to become malignant. The technique could possibly be used for assessing pre-malignancy, since such cells might not be so "dominant" as those from normal controls.

To conclude, as Emery says,[2] medical genetics seems likely to become the preventive medicine of the future, and the subject may also be of great value from the standpoint of epidemiology.

I am grateful to Messrs Edward Arnold for allowing me to draw freely from my book *Human Genetics and Medicine* (1970) for part of this paper.

Further Reading

In addition to the books mentioned in the references below, the Department of Health publish a booklet called *Human Genetics*. A new edition will be available in 1972.

This article is based on a lecture given in the Birmingham course under the title "The Scientific Basis of Clinical Practice" (see B.M.J. 27 November 1971, p. 510).

References

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Clinical Endocrinology

Male Infertility

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Unwanted sterility is a problem in about 10% of the marriages in this country. In between one-third and one-half of these an abnormality can be found in the male partner. The identification of the reason for the infertility is based on both clinical assessment and laboratory investigation. Only when the type of abnormality is known can further treatment be considered.

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Assessment of the Patient

CLINICAL

Those aspects of the history and physical examination specifically relevant to the problem are set out in Table I. Though in normal subjects, conception has almost always taken place within six months of trying for children, it is usual to allow up to a year of infertility before undertaking a full investigation; an exception to this approach is made when the wife is in the late 30s and so is reaching the end of her reproductive life. In this instance it is advisable to perform laboratory studies after a three months' history of sterility.

It is most important to inquire about the frequency and timing of intercourse, as these factors can occasionally provide a simple explanation for the infertility (see section on causes). The frequency of erections and shaving gives some indication