The Genetic Counselling Clinic at a Children’s Hospital

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SUMMARY

With the decline in the clinical frequency of infectious and nutritional disease there is an increased importance to the clinician of genetically regulated patterns of disease. Most clinicians are unable to spare the time, or are disinclined to adopt an approach formally orientated towards genetics, and the role of the geneticist in clinical situations is becoming increasingly apparent.

Fifty years after the foundation of the Transvaal Memorial Hospital for Children, a Genetic Counselling Clinic has been instituted. Counselling principles, and the estimation of risk figures, naturally vary with the various patterns of inheritance. There has been considerable recent expansion in the fields of cytogenetics and antenatal diagnosis, and both of these bear heavily on modern techniques of counselling.


Paediatrics embraces the welfare of the unborn child, and, furthermore, the welfare of the prospective child.

Moncrieff, 1946.

Over the past 30 years infectious and nutritional diseases have substantially been conquered in the developed countries. The relative importance of disease due wholly or in part to genetic causes has consequently assumed increasing significance. Diseases like otitis media, rickets and other sequelae of infectious and nutritional diseases have virtually disappeared from the wards of children’s hospitals in these countries.

As far as we are aware no comparable figures exist for any South African hospital, but Carter has presented data to show that at the Hospital for Sick Children, Great Ormond Street, London, environmentally determined diseases accounted for two-thirds of all deaths in 1914, while 40 years later (in 1954), only one-seventh of deaths at the same hospital were due to such diseases. During these same years the proportion of deaths due to wholly genetic causes increased from 2% to 12%, while the partly genetic causes increased from 14.5% to 25.5%.

Genetic causes of death may not, however, give a valid indication of the magnitude of the problem of genetic disease within the community. At a recent Conference on Genetic Disease Control it was said that 9.3% of inpatients in a children’s hospital had been admitted because they had diseases of clearly defined genetic content, and another 18% of the admissions were the result of congenital malformations. These figures relate to a teaching hospital in the United States and it was pointed out that the figures would probably be significantly lower for non-university hospitals.

It is fair to assume than in the principal children’s hospital for Whites in Johannesburg (because here are to be found the people and the facilities to investigate and treat such patients), the proportion of children admitted with genetic diseases will probably approach 30%.

NEED FOR A GENETIC COUNSELLING CLINIC

We have argued that the problem of genetic disease in a children’s hospital is anything but a small one, and must now consider whether a genetic counselling clinic, staffed by someone specializing in medical or human genetics, is an essential facility at every paediatric hospital. Ideally, the family doctor or the paediatrician should be the person giving the counselling to the patient or his family. The doctor in charge of the case is well placed to answer the questions about aetiology and prognosis as well as those of a genetic character as they relate to other family members. Unfortunately, most general practitioners and paediatricians are not able to provide this genetic counselling, for a variety of reasons: among them lack of training (co-ordinated comprehensive human genetics teaching is sorely deficient at our University) and shortage of time, due to the extreme pressure placed upon the overworked clinician.

Roberts has suggested that good genetic counselling or, as he called it, ‘genetic prognosis’ depended on 3 things: diagnosis, the individual family history, and the background of the literature. The initial diagnosis is usually made by a paediatrician or even the general practitioner; but because of the experience of the medical geneticist in seeing genetic diseases, many of which are extremely rare, he too can play an important part. The diagnosis may in some cases become apparent only when a detailed family history has been elicited; and the taking of such a family history is often a very time-consuming affair requiring skills acquired by a geneticist over many years. It is imperative that as much attention be paid to family members
who apparently do not suffer from the disease as to those who are obviously affected by it.

Although the medical geneticist will not have everything at his finger-tips, he will know where to look for information and will probably have more time than the clinical specialist to do so. It is not only a question of locating the background literature; there is also the matter of assessing it. Studies vary in quality. It is thus mandatory that the genetic counsellor be able to make a critical assessment of the literature. To be able to do this, training in basic genetic principles is probably required as well as a familiarity with some of the sophisticated statistical techniques which are such an integral part of human genetics.

Towards the end of 1972 Professor J. D. L. Hansen, Professor of Paediatrics, University of the Witwatersrand, took the initiative in setting up a Genetic Counselling Clinic at the Transvaal Memorial Hospital. It is staffed by 2 medical geneticists, a senior registrar in paediatrics, and a psychiatrist interested in inherited diseases; 2 social workers also participate. Cases are referred by members of the staff of the Transvaal Memorial Hospital and the Queen Victoria Maternity Hospital, as well as by private practitioners. We feel that this Clinic will cater for patients with genetic problems falling into categories different from those presenting at the Clinic, which is run jointly by the Cytogenetics Unit and the Human Serogenetics Unit at the South African Institute for Medical Research, at which we counsel people who often have a relatively minor genetic abnormality, and others who know of the existence in the family of some real or suspected genetic defect.

Prospective parents who come to the Clinic are anxious to know the probability that afflicted children will be born to them. Sometimes related individuals who are considering marrying one another seek counselling; but the commonest reason for seeking genetic counselling at a children's hospital is the birth of a child with a serious defect which may be totally or partially genetic in origin.

During the first 3 months of 1972, a total of 202 cases were referred to the Cytogenetics Unit of the South African Institute for Medical Research. From Table I it will be seen that 98 referrals were either of parents seeking advice following the birth of an abnormal child, or of infants in whom an abnormality had been diagnosed by the clinician, who requested cytogenetic investigation. Private practitioners referred 21 of the White cases, and the Transvaal Memorial Hospital a further 21, while 10 were sent by other hospitals. The balance was made up of 40 Bantu referred by Baragwanath Hospital and 6 Coloured and Indian cases from Coronation Hospital.

**PATTERNS OF GENETIC DISEASES**

**Recessively Inherited Diseases**

Parents may have one or more normal children and then produce a child with a recessively inherited condition. Particularly when it is the firstborn child who is so affected the anguish may be considerable, and it is not lessened when they have to be told that any pregnancy upon which they embark carries a 1 in 4 probability of resulting in the birth of a similar affected child.

The presentation to the parents of these odds is possible because having produced an affected child they have demonstrated that both carry the same mutant or abnormal gene. An experienced counsellor will not, however, boldly state the probability and leave it at that. He will go on to explain to the couple that we all carry approximately 5 to 8 deleterious genes, and that most of us are fortunate enough to marry someone who carries a different set of mutant genes. The likelihood of the same deleterious gene existing in both members of a married pair is, of course, significantly greater when they are blood relatives but even in this situation the risk is not all that high. It may be pointed out that in a White population the risk is no greater than that for haemolytic disease of the newborn, due to Rhesus incompatibility when a Rhesus-negative woman marries a Rhesus-positive man, which is 1 marriage in 7. When there is nothing in the family history to suggest that a recessively inherited defect has occurred it does not seem to be irresponsible or foolish for cousins to marry and produce children.

Parents who have produced a child suffering from a severe recessive disease are often anxious for the future of their apparently normal children. When she grows up what will be the chances of her producing a child with the same disease? is a common question in their minds, even if it is not expressed. If the disease is a rare recessive, one is able to reassure them that, provided a carrier daughter marries a normal man, the likelihood is not very great even if it is greater than that for a normal couple. The recessive sufferer can only pass on 1 mutant gene to a child, and the likelihood of marrying a heterozygote (or carrier) is of a low order. In the case of cousin marriage the probability of both being carriers is, however, considerably increased.

Parents are also often anxious about the future marriage history of an apparently normal child. If the carrier cannot be identified the counsellor can only give a probability

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>No.</th>
<th>Results of karyotyping</th>
</tr>
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<tbody>
<tr>
<td>Down's syndrome</td>
<td>35 Trisomy-21</td>
<td>24 cases</td>
</tr>
<tr>
<td></td>
<td>Mosa/c [46XX, 47XXG+]</td>
<td>1 case</td>
</tr>
<tr>
<td>Translocation</td>
<td>[46XX,D-,t(DqGq)]</td>
<td>2 cases</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>8 cases</td>
<td></td>
</tr>
<tr>
<td>Multiple congenital abnormalities</td>
<td>22 Normal karyotype</td>
<td>20 cases</td>
</tr>
<tr>
<td></td>
<td>E'</td>
<td>1 case</td>
</tr>
<tr>
<td></td>
<td>D'</td>
<td>1 case</td>
</tr>
<tr>
<td>Intersex</td>
<td>19 cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>46 Xi (Xq)</td>
<td>1 case</td>
</tr>
<tr>
<td></td>
<td>45X</td>
<td>1 case</td>
</tr>
<tr>
<td></td>
<td>47XXX</td>
<td>Twin</td>
</tr>
<tr>
<td></td>
<td>45X, 46XX</td>
<td></td>
</tr>
</tbody>
</table>

These patients were referred during the first 3 months of 1972, and represent nearly 40% of the 202 cases referred during the period.
It seems likely that the mutation has taken place in the gonad of one of the parents. The parents will want to know the recurrence risk for future children. A precise risk figure cannot be given, but it is probably true that the risk is low, in the order of about 1 in 10. The recurrence risk figure for the children of such affected individuals is the same as for the children of an individual with the non-sporadic variety of a dominant disease, namely 1 in 2.

Sex-linked Diseases

The function of most of the DNA of the human Y-chromosome is not known. The X-chromosome, in contrast, is crowded with genes with a great variety of functions. The majority of diseases determined by these genes are X-linked recessive; the hemizygous male carrying one of the genes will manifest the disease, while the female will only possess the disease if she has inherited the mutant gene from both her parents, i.e. if she is homozygous. The female carrier of the gene for haemophilia is usually unaffected, but there is a 1 in 2 chance that her male child will suffer from haemophilia and the same chance that a female child will be a carrier. In the case of X-linked dominant diseases a female heterozygote will herself suffer from the disease and there is a 1 in 2 probability that all her children will also be affected. Occasionally problems are encountered when trying to decide whether a particular female is or is not a carrier of, for example, the gene for haemophilia. But, by and large, the counselling of a family in which haemophilia occurs is quite straightforward. It is possible to use antenatal diagnosis of the sex of the foetus, and to allay fears about the birth of an affected child if it is shown that the mother is carrying a female foetus. Unfortunately, there is at present no way of showing whether a male foetus is a haemophiliac.

Polygenic Inheritance and Common Congenital Abnormalities

Congenital abnormalities like cleft lip and palate, pyloric stenosis, dislocation of the hip, talipes equinovarus, spina bifida and anencephaly are more common than simply inherited conditions. Although genetic factors are undoubtedly involved in the causation of these diseases, environmental influences also play a part. Because the modes of inheritance do not conform to simple genetic patterns, parents who have produced an affected child have to be counselled on the basis of empirical risk figures. These figures have been compiled from large-scale family studies and enable the counsellor to do a part. Because the modes of inheritance do not conform to simple genetic patterns, parents who have produced an affected child have to be counselled on the basis of empirical risk figures. These figures have been compiled from large-scale family studies and enable the counsellor to tell the parents the risk of recurrence in subsequent children after they have produced one or more affected offspring.

Environmental factors are thought to play an important role in the production of these congenital malformations, and if they could be identified, individuals known to be at risk could theoretically be protected from them. Empirical risk figures can only be used with confidence when counselling individuals drawn from the population providing the families for the calculations. Empirical risk

Dominantly Inherited Diseases

Although it is a disease of extreme rarity in other parts of the world, porphyria variegata is probably the commonest autosomal dominant disease in South Africa. Dr Geoffrey Dean, by tracing the genealogies of affected individuals, showed that this was due to 'founder effect' one type of random genetic drift. The disease generally only becomes manifest after puberty. However, an anxious parent suffering from porphyria may want to know whether his or her children have inherited the mutant gene. It is not usually possible to give a confident answer to such a query, but here she may be told that the probability is 1 in 2, or 50%. It is probably a wise precaution to warn against the taking of certain drugs until such time as the child is old enough for the diagnosis to be excluded with confidence.

Because all genes probably interact with all the other genes possessed by an individual they do not always produce the same effect in all individuals. It is obvious that in order to construct an accurate pedigree all family members will have to be carefully examined.

Some dominantly inherited diseases exhibit the phenomenon of the 'skipped generation'. A child may present with a disease known to be inherited as a simple Mendelian dominant, but from which neither parent had suffered. If a poor family history is obtained the counsellor might suppose that he is dealing with a new mutation. If a complete history is taken it will emerge that a grandparent, for instance, suffered from the same disease. It is now apparent that one parent does carry the gene responsible (in whom it is said to be non-penetrant), and each child of his carries a 1 in 2 risk of inheriting it from him.

Sometimes a dominantly inherited disease appears in a child without a history of its having been present in the parents or their families. This is known as a sporadic case.
figures for South African populations are sadly lacking, and we are reduced to using Western European figures when counselling Caucasoids. The situation with respect to Negroes is even more precarious. One of the research aims of our genetic counselling clinic is to assemble data from which empirical risk figures can be obtained.

**Chromosomal Anomalies**

The majority of chromosomal anomalies arise as fresh mutations involving either numerical or structural aberrations of autosomes or sex chromosomes. Thus, cases of Turner’s syndrome—45X and variants, Klinefelter’s syndrome—47XXY and the 47XYY syndrome are only rarely found in more than 1 member of the same family. Counselling is therefore of very limited use, except to explain to anxious parents the mechanism involved in the production of the disease, to reassure them about recurrence risks based on empirical risk figures and to give a prognosis as to the future development of the affected child.

Chromosomal abnormalities can also be responsible for numerous varieties of multiple congenital anomalies. In a 5-year study of cases referred to the Cytogenetics Unit for chromosomal analysis of children born with multiple congenital anomalies, 25% of all the cases investigated (albeit a biased sample), have been found to suffer from numerical abnormalities. Structural abnormalities such as deletion syndromes were found in a minority of the above 25% of cases.

In a proportion of these cases it may be found that a parent carries a balanced translocation or an abnormal marker chromosome which is responsible for the anomaly. Cytogenetic investigation of all parent as well as of the propositi is therefore essential. This emphasizes the need for genetic counselling services to be available at all hospitals.

Because there is no way of telling from the appearance of a child with Down’s syndrome whether it is due to the more commonly occurring non-disjunction type of trisomy-21, or to the rarer unbalanced translocation type, it is mandatory for the paediatrician to obtain a karyotype on all cases of Down’s syndrome (Table I). When the latter type is found to exist, the monitoring of future pregnancies with antenatal chromosomal analysis, and, if necessary, elective termination of pregnancy can be offered.

The presentation of risk figures to parents should always be accompanied by an indication of the likelihood of a serious genetic disease presenting in a child born to a couple with no family history of an abnormality. Roberts’ gives this risk as about 1 in 40.

**RECENTLY DEVELOPED AIDS TO COUNSELLING**

**Antenatal Diagnosis**

It can confidently be claimed that the successful introduction and perfecting of the technique necessary for the antenatal diagnosis of a large number of genetic diseases represents one of the most significant recent advances in medical genetics. The premariage detection of all carriers of the genes responsible for recessive diseases (both autosomal and X-linked), followed by the monitoring of all pregnancies of carrier couples and abortion of the affected foetus, should eliminate that disease in the population. For economic reasons mass screening would initially be offered to populations known to have a high frequency of the gene.

In Table II are presented a number of cases in which antenatal diagnosis has been performed. It will be seen that the majority were carried out for chromosomal karyotyping—to exclude cases of Down’s syndrome being born to a couple who have already had an affected child (or one of whom is a translocation carrier), or else to an elderly mother.

**Value of Linkage Relationships in Counselling**

There are certain genetic diseases, usually dominants, which only become apparent when adulthood is reached. An example of the usefulness of linkage is provided by dystrophia myotonica, a dominantly inherited disease which in many families only becomes manifest in adulthood. The close linkage of its locus (called *Dm*) with the secretor locus (*Se*) has provided hope that in a certain proportion of families in whom the *Dm* and *Se* genes are segregating, study of the secretor status will enable an estimate to be made of whether the gene for dystrophia myotonica is present or not; and this, of course, in a child before the disease has manifested itself. Because the secretor status of a foetus can be determined from the amniotic fluid, it is possible in such families to estimate the probability that the unborn child carries the *Dm* gene.

Jenkins *et al.* have recently described how the segregation of alleles responsible for glucose-6-phosphate dehydrogenase can be of use in deciding whether certain Negro females are or are not carriers of the haemophilia gene.

**AN ASSESSMENT OF THE VALUE OF GENETIC COUNSELLING**

The Genetic Counselling Clinic at Transvaal Memorial Hospital is in its infancy, and it is impossible at this stage to make any assessment of the usefulness or otherwise of the role it plays in the practice of medicine in Johannesburg. Having given a couple the risks of subsequent children with a certain disease being born to them, it may be asked how they will act. Roberts* and Carter* found that two-thirds of their 'high risk families' were deterred from having future children, and one-quarter of their 'low risk families' were also deterred. This latter finding was somewhat disconcerting, and caused Carter* to modify his technique. We feel that the unsatisfactory finding in the follow-up might be due to their practice of seeing the parents only once. Fraser Roberts* felt that this might be the case, and so at our clinic we insist on seeing the patients at least twice and arrange a 'follow-up' visit by a social worker 2–3 months later. In this way we hope
TABLE II. PARTICULARS OF 30 EXAMINATIONS OF AMNIOTIC FLUID FROM AMNIOCENTESIS RECENTLY CARRIED OUT BY THE CYTOGENETICS UNIT OF THE SAIMR

<table>
<thead>
<tr>
<th>Indications for amniocentesis</th>
<th>No. of patients</th>
<th>Weeks of gestation</th>
<th>Karyotype</th>
<th>Nuclear sex</th>
<th>Enzyme activity</th>
<th>Outcome of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents heterozygous carriers of Tay-Sachs disease</td>
<td>1</td>
<td>16-18</td>
<td>46XX</td>
<td>+ve</td>
<td>Normal</td>
<td>Normal female</td>
</tr>
<tr>
<td>Previous child with Down's syndrome</td>
<td>3</td>
<td>16</td>
<td>46XX</td>
<td>+ve</td>
<td>Normal</td>
<td>Normal female</td>
</tr>
<tr>
<td>Increased maternal age</td>
<td>4</td>
<td>16</td>
<td>46XX</td>
<td>+ve</td>
<td>Normal</td>
<td>Normal female</td>
</tr>
<tr>
<td>Previous child with microcephaly</td>
<td>1</td>
<td>16</td>
<td>46XX</td>
<td>+ve</td>
<td>Normal</td>
<td>Normal female</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
<td>1</td>
<td>16</td>
<td>46X(Yq)</td>
<td>-ve</td>
<td>Normal</td>
<td>Normal male</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>2</td>
<td>16</td>
<td>46XY</td>
<td>-ve</td>
<td>50% risk males</td>
<td></td>
</tr>
<tr>
<td>Hunter-Hurler syndrome</td>
<td>1</td>
<td>18-20</td>
<td>46XY</td>
<td>-ve</td>
<td>Normal</td>
<td>Normal male</td>
</tr>
</tbody>
</table>

The enzyme activity estimations were performed by the Human Serogenetics Unit and were confirmed by J. O'Brien (Tel Hashomer). Figures in parentheses refer to cases of which the outcome is awaited. It will be noted that the antenatal diagnosis or exclusion of Down's syndrome, on the grounds either of a previous child with the condition or of increased age of the mother, makes by far the largest single group, with suspected Tay-Sachs disease next in size.

CONCLUSIONS

Although it was nearly 50 years before a Genetic Counselling Clinic was established, the Transvaal Memorial Hospital cannot be said altogether to have neglected genetic counselling in the past. Many paediatricians have counselled their own patients and their families, and some have sought the advice of the genetic counsellors at the South African Institute for Medical Research.

It is not anticipated that the Clinic will take over all this work. Paediatricians should be encouraged to counsel all families with straightforward genetic diseases; they have been invited to refer to the Clinic families with diseases of complex genetic aetiology and families in which the inheritance of a disease does not conform to the usual genetic pattern. Some busy paediatricians may feel, after making an accurate diagnosis, that assistance is needed in taking the family history or assessing the background literature, and this is where the Genetic Counselling Clinic comes into the picture. Perhaps more than in any other speciality within paediatrics the genetic counsellor is a member of the team existing for the more expert handling of a sick child and his family, including, uniquely perhaps, prospective siblings.

We are grateful to Professor J. D. L. Hansen and the Superintendent of the Transvaal Memorial Hospital, Dr Ruth Drubin, for expediting the establishment of the Genetic Counselling Clinic. The Director of the South African Institute for Medical Research, Professor J. H. S. Gear, and the Deputy Director, Professor J. F. Murray, gave us (T. J. and E. W.) every encouragement in setting up the Clinic, and have generously provided facilities for the many laboratory investigations so essential to this work. Without the enthusiastic co-operation of Dr Benny Kertzner, Paediatrician assigned to the Clinic, Dr C. Irwin, Psychiatrist, and Mrs C. Bloom and Mrs J. Kronberg, Social Workers, the smooth running of the Clinic would not be possible or certainly not nearly so efficient.

REFERENCES