GENETIC COUNSELLING AND LOOKING TO THE FUTURE

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What I am going to say about genetic counselling is based on the experience I have had with Dr Fraser Roberts at Great Ormond Street over the past ten years or so. As it is a children's hospital, obviously a great deal of our counselling has been in relation to congenital malformations, although many other things have been included. The parents who come for genetic counselling may be placed in three groups. The largest group is of parents who are healthy themselves and have had a child or perhaps two children with some malformation or children's disorder. The second group is that where one or other parent himself has some disorder; perhaps one parent is an achondroplastic or has tuberose sclerosis or hare-lip. The third group consists of cases where there is no malformed child and the parents are healthy, but there is something rather alarming in the family history. Perhaps the mother had a brother who had Duchenne-type muscular dystrophy.

We have certain principles in genetic counselling, of which perhaps the most firm is that it is not our job to tell the parents what to do. We try to tell them the odds honestly, as best we know them, and also try to put the risks in perspective, telling them that something like one child in 50 is born with quite a serious malformation anyhow and that any additional risks must be seen in that perspective. Some parents really do need to be told what to do, but the best person to do that is the family doctor, who knows the family much better than we can do after seeing them once. So when the parents do have to be told, we usually pass the responsibility back to him. Genetic counselling has more than one object. Not only must the parents have the information they need and have specifically asked for, but in addition there is the increasingly important medical point of view. Knowing in advance that a particular child as yet unborn, perhaps not yet conceived, runs a particular risk of some disease or malformation may be a great help in getting early diagnosis and early treatment. There has in the past been a tendency to regard genetic disorders as untreatable. That is becoming less and less true, but any treatment usually has to be started early and continued with considerable determination.

Risks in mongolism

What kind of odds does one give to parents? Fortunately, the high-risk conditions by and large are rare, and they are the condi-

tions which are almost entirely genetically determined. Such conditions may be due to chromosome mutations, about which Dr Clarke has already told us something, or to gene mutations, dominant, recessive or sex-linked recessive. With chromosome mutations, the risk of recurrence in later children is fortunately usually pretty low. The non-disjunction, or whatever is responsible for the condition, has occurred to a normal mother or normal father, and it has occurred in the actual formation of the ovum or the sperm, so that the risk of recurrence is small. We have long known, for example, that where one mongol has been born the chance of parents having a second mongol child is only of the order of one or two per cent. If the mongol child himself or herself has a child, that is a very different matter. This has always happened to mongol girls so far; of 10 children born to them five have also been mongols. A mongol woman has three 21-chromosomes and so when she forms an ovum she is likely to pass on either one or two. If one is passed on the result is a normal child, but if two are transmitted another mongol is born. But for later brothers and sisters of a mongol child the overall risk is only one or two per cent and one must put that into the perspective of the random one in 50 risk of a serious malformation. It is an additional risk, but still not a high one. We had, of course, always been unhappy about certain individual families where the risk appeared to be higher, and we have been enormously helped here by chromosome studies on the parents. This is particularly important when the mother is under 30. As I have said, the risk of a second mongol child is between one and two per cent, but that is above the random risk to an extent which depends on the mother's age. Any woman of 40 has a one per cent risk of having a mongol child anyhow, and a woman of 45 has a two per cent risk of having a mongol child, quite apart from any family history. If in fact a mother has had a mongol child at 40, the subsequent risk is really very little increased over the random risk; for a woman of 20 who has a mongol child the recurrence rate is still one to two per cent, but for any other woman under 25 the risk of mongolism would be about one in 2,000. We had suspected that particularly in this group of young mothers of mongols there was a small high-risk group. Chromosome studies have enabled us to pick out some of these cases where one or other parent—it is not always the mother—has a chromosome abnormality such that there is a high risk of a second mongol child.

This was rather vividly brought home to me in a follow-up of mongol families. There were five mothers in a rather large group who had had a second mongol child during the follow-up. In two, this was not surprising because the mother was over 40 when she had the first mongol child and she therefore was a high-risk case

because of her age, but three were young mothers and it was sad and disappointing that they should have had a second mongol child. In all three families there was an explanation. In one case the mother had a 15-21 translocation. This was discovered subsequently, so we could not help her, but it is nice to know that we could have helped if the condition had been found sooner. In the second case the mother had a 21–22 translocation, and in the third case the father showed a curious mixture of translocation and mosaicism. Knowing what I know now, I could have warned all three of those couples that there was a high risk of having a second mongol child. However, even in the group of mothers under 30 we are finding a chromosomal anomaly in only about one in 50, so that in 49 out of 50 cases the risk of further mongols is small. For the one in 50 with a parental anomaly you have to assign a risk appropriate to what you find. For example, if the mother has a 15–21 translocation, the chance of any subsequent pregnancy giving rise to a mongol is about one in three, which is a very appreciable risk. If the father has the 15–21 translocation, the chance of a second mongol child is very much less, but he is likely to have daughters with the translocation who may produce a mongol in later generations. With translocation, of course, we do examine other members of the family; on two or three occasions we have found that a sister of the mother of the mongol, perhaps herself not married yet, or without children, has the same translocation as the mother of the mongol and therefore a high risk.

Another thing one has to look for is mosaicism. We have not come across a case yet in genetic counselling, but no doubt we shall. With these it is going to be rather difficult to know the risk, because the proportion of normal and mongol cells in different tissues seems to vary quite appreciably with the tissue. What is really relevant to the risk to the child is what is going on in the ovary, and we do not know what is happening there, so that all we will be able to say in general is that there is an increase in the risk in mosaicism. Chromosome studies probably do not entirely solve the problem, for even without the known cases where a parent has a chromosome abnormality, there is still an increase over the random risk in young mothers. We suspect that we are missing cases of mosaicism, though there could be other explanations. However, chromosome tests are an enormous help, and I would never give genetic advice in cases where the mother is under 30 without having a chromosome test on both parents. The parents need to be tested rather than the child, though it is nice to investigate the child as well. With the sex chromosome abnormalities this problem arises less. Persons with Klinefelter's XXY and Turner's XO patterns are sterile, so the question of reproduction does not arise. Curiously enough, in the

case of triple X women, whom one might expect on the analogy of mongolism 21–trisomy to be at risk of having children either triple X or boys with Klinefelter's syndrome, this does not seem to happen. Triple X women seem always just to pass on one X chromosome and have normal children, which is very fortunate; in fact, by and large with sex chromosome abnormalities one can be encouraging about further children, for the risk of recurrence is low.

Risks with dominant mutant genes

If you are dealing with a condition due to a dominant mutant gene, that is, one which always causes the condition in the heterozygote as in achondroplasia, genetic counselling is rather simple. If normal parents have an achondroplastic child, one can be pretty sure that that child has been affected as the result of a fresh gene mutation, and there is little risk to further children. However, that child himself has the mutation, and there is a one in two chance of his transmitting it to his children; that is a fairly high risk and if anybody asks he should be told just what the risk is. To cite an actual case, five years ago an achondroplastic woman came to the genetic clinic because her recently born first son was an achondroplastic like herself. Nobody had warned her. She had had this child by caesarean section, and she wanted to know what the risks of having another were. We told her just what they were, and she badly wanted one more child. She had one more and I am glad to say that that second child is normal. As regards the future the normal son need not worry, but the achondroplastic son has a one in two chance of his children being achondroplastic.

You cannot do anything for achondroplasia, but with other conditions the genetic risks have medical implications; for example multiple polyposis of the colon undergoes malignant change in adult life. Children of individuals with multiple polyposis need regular sigmoidoscopy so that the one in two who develop the condition may be detected as soon as polyps develop and have a total colectomy before the condition becomes malignant. Sometimes with these dominant conditions it is necessary to make sure that both parents are really normal before giving a good risk for further children. In tuberose sclerosis, for example, a mother may have very little abnormality except for the adenoma sebaceum of the face. If she has got that she has the gene and there is a one in two risk to any children.

Cystic fibrosis of the pancreas

With autosomal recessive conditions things are again fairly straightforward. The most significant one, which the Americans perhaps would call a congenital malformation but which we might

not, is cystic fibrosis of the pancreas. This is the commonest serious recessive condition in this country, affecting about one child in 2,000. With recessive conditions, the usual history is that two parents, by bad luck or because they are cousins or blood relations, produce one defective child; from then on there is a one in four risk to later children. I usually put it the other way round; the odds are three to one on a child being all right. With cystic fibrosis of the pancreas this knowledge is medically valuable; a sweat test made at about six weeks will show if the child at risk is or is not affected. If it is affected, we must do our very best to see that the child does not get any permanent lung damage from pulmonary infection.

With these recessive conditions it is important to reassure the parents about the other unaffected children, telling them that there is little chance of its appearing in any grandchildren. There is little risk that the unaffected brothers and sisters, though two in three will carry the gene, will have an affected child because to do so they must be unlucky enough to marry another carrier of that particular recessive gene; this is unlikely unless they are unwise enough to marry a cousin.

Heterozygotes for recessive genes

Probably most of us are heterozygote carriers for two or three quite serious recessive genes, but most of us are lucky enough to marry a spouse who carries two or three quite different ones. Genetic counselling is increasingly helped by the existence of tests for heterozygotes. The sibs of, say, children with phenylketonuria can be tested to see if they are carriers of this gene and, if they are, their prospective spouses can also be tested. In one family we had recently, the parents had had two children with phenylketonuria, a girl and a boy who were fourth and fifth in the family. The three older boys in the family were an intelligent group of adolescents, and they wanted to know if they were heterozygotes. All three of them were, and the first two have now brought their fiancees along for a test to see if they are also carriers of the gene concerned. Another similar case was that of a mother who had had two children with phenylketonuria, one a rather hopeless mental defective but the other doing very well because of early diagnosis. She lost her husband and was going to marry again but wanted a test done on the prospective husband; he was tested and found not to be a carrier, and she knows there is no risk of phenylketonuria turning up in this second family.

We would dearly like a test for heterozygotes for cystic fibrosis of the pancreas but we have not got it yet. Some optimistic claims were made for the sweat sodium and chloride test. This is very good for detecting homozygotes, but really no good at all for heterozygotes

because the overlap with normals is far too great. A particular recessive condition can be a real public health problem, as cystic fibrosis almost is in this country, though far less than the sickle-cell anaemia found in parts of Africa or Cooley's anaemia in parts of Italy. These kill one child in 100 in certain districts compared with our one in 2,000 for cystic fibrosis of the pancreas. With a one per cent incidence it becomes worth while to think of tests for heterozygotes as a public health procedure. In areas of high incidence of Cooley's anaemia, for example in Ferrara where wards may contain 10 or 20 of these children with this lethal anaemia, very logically the Italians have made tests for the heterozygote part of the ordinary routine school medical service. All the heterozygous carriers, about 20 per cent of the school population in these areas, are known, and with the co-operation of the local priest the medical services will do their best to see that they do not marry each other. If they are successful in this, they will wipe out their biggest paediatric problem. I am quite sure that Africans in the areas of high incidence of sickle-cell anaemia are going to do just the same thing. Already in America, for example, coloured people are demanding this test to see if they are heterozygous or not before they think of marriage. And if they are they have their spouse tested too.

The essential risk with recessives is the one in four risk to later brothers and sisters, there is little risk to other members of the family.

Sex-linked recessive genes

Sex-linked recessive conditions are a special group because the woman has two X chromosomes, so if she has the mutant gene on an X chromosome she is heterozygous for the mutant gene. She is protected by the presence of a normal gene on the other X chromosome. A man with only one X chromosome and a little Y chromosome, with few or perhaps no genes corresponding to those on the X chromosome, is not protected and if he has the mutant gene on the X chromosome, he is clinically affected. Genetic counselling here is fairly straightforward. If a mother comes to you with a boy suffering from Duchenne-type muscular dystrophy, or nephrogenic diabetes insipidus, or haemophilia, or Christmas disease, and has any other male relative affected, then you know that she is a carrier. If, for example, she has two boys or a brother or an uncle with the condition, then you know that the boy has not been affected by a fresh mutation and that the mother is certainly a carrier. There is a one in two risk to later sons of being affected, and a one in two risk to any daughters of being carriers like herself. There are difficulties though, when as in about one-third to half the cases of haemophilia or Duchenne-type dystrophy a mother comes and says she has one boy with the condition but no other male relative in the family is

affected. There are two possibilities. One is that the boy has been affected as the result of a fresh mutation; the mother is not a carrier at all, and she can have a dozen more boys and none of them will be affected. The other possibility is that the mutation occurred at least one generation back and that the mother is a carrier although no other of her relatives are; in this case there is a one in two risk to further sons. We know on empirical grounds that in these situations the mother is more likely to be a carrier than not. The chance is about two to one, and so we can give an empirical risk for later sons of about one in three. This is unsatisfactory, however, because about one in three of those mothers is not a carrier at all and there is really no risk; here again, some test for the heterozygous state in the carrier mother is extremely useful. In one of the rarer conditions, the congenital renal tubular defect of nephrogenic diabetes insipidus, a simple urine concentration test on the mother enables us to pick out the heterozygous woman with a fair degree of reliability. These women are not clinically affected like their boys, but they produce urine with a specific gravity of about 1012 after a night without fluid. The carrier women in a family can thus be detected once you have picked up one case, and we can tell them of the risk to their sons and also tell their family doctors.

Early diagnosis is important here. These children tend to die in the first year, or to be left with quite severe mental defect, unless they are given a great deal of fluid from birth onwards. They need plenty of fluid to drink four-hourly and this must go on during the night. The outlook is very good if the diagnosis is made soon after birth.

There was rather a sad story earlier this year. The mother of one of our patients at Great Ormond Street with this condition was found to be a carrier; she has two sisters, one of whom is a carrier and the other is not. The one who is a carrier lives somewhere in the Midlands, and I wrote to her family doctor and told him of the one in two risk to the sons of that particular woman. The first child she had was a girl, the second a boy who was normal, and the third was born this spring. In the intervening three or four years I think the family doctor had forgotten what I had said or lost my note. The child did not thrive and was sent to hospital. It was there for a week before it was seen by a paediatrician, who then made the diagnosis; but it was too late and that child died. A blood electrolyte test done shortly before he died showed an enormous hyperelectrolytaemia, and the whole history was typical of nephrogenic diabetes insipidus. If I had kept better contact with that family that child would have been all right. The family doctor would have sent a child into hospital with a ready-made diagnosis and the hospital would have got a paediatrician in quickly.

With Duchenne-type muscular dystrophy, possible carrier women

want to know their situation badly. A girl who has seen her brother go off his feet by 11 and die by 20 is understandably concerned. There are hopeful indications here. It was claimed that the serum aldolase level, which is very useful in the early diagnosis of muscular dystrophy, picking out the affected boys long before they show any signs or symptoms of the disease, would help to pick out heterozygous mothers. Unfortunately, it is really of no use at all. Some workers in Switzerland have claimed that another serum enzyme, creatine-phosphokinase, is helpful in picking out the majority of carrier mothers; we have been doing some work on this with the chemical pathology department at the hospital for such disorders and other centres are finding them useful too.

Genetically complicated conditions

Most of the common malformations are much more complicated genetically. What one is dealing with is a genetic predisposition needing environmental triggers, again unfortunately of a kind mostly unknown, before the child develops the malformation. By family studies, we can, however, develop quite useful empirical risk figures which we can give to parents and which not only help them but may also help in early diagnosis. With most of the common malformations the recurrence risks are in general fairly low, but there may be individual families with relatively high risks. To take quite a simple example, when we came to follow up the children of early survivors of Ramstedt's operation for pyloric stenosis who had had their operations 20–40 years ago we found a relatively high risk, of about one in five, to the sons of women who had had pyloric stenosis as children. There are five boys for every girl with pyloric stensosis, but it is the girl with pyloric stenosis who later runs a high risk of having an affected son. The risk is sufficiently high for it to be true that if a boy starts vomiting in the first four months of life, whereas normally pyloric stenosis would be low on your diagnostic list, that child should be regarded as having pyloric stenosis until you have proved otherwise if the mother has a Ramstedt scar.

With hare-lip and cleft palate, the risk to sons and later brothers and sisters is fairly low, only of the order of one in 25 to one in 30, but where the parent and one child are already affected it goes up to about one in seven or one in ten. Why that should be so we do not quite know. I suspect it is because the man has been unlucky enough to marry a wife with the same genetic tendency.

Dr Laurence has told you that the recurrence risk for central nervous system malformations is of the order of one in 25, which is not high but is also certainly not negligible. After a woman has had two children with a major central nervous system malformation it rises to one in seven or eight, and that is a risk of which the mother

who asks you should be told. It is then up to her whether she takes the risk again or not.

With congenital heart malformations, there is fortunately a low risk of recurrence, probably of about one in 40 where parents have had one affected child. How much the risk increases if they have had two children with congenital heart malformations we do not yet know. I give a figure of about one in ten, but this is not based on any good series yet. It will take some time to collect one, and as more and more surgery is done in these cases, risks will be quoted in terms of specific malformations rather than congenital heart disease as a whole. We have just studied a series of children with aortic stenosis, and the risk there is rather higher, of the order of one in 25.

For Hirschsprung's disease, the overall risk of occurrence is not high, and for the short segment cases it is only about one in 20 for sons and about one in 100 for daughters; with long-segment cases (we do not quite understand this) there is a considerably higher recurrence risk of the order of one in ten, irrespective of sex. For the rare very long segment cases, with involvement right up to the duodenal junction, there may even be a one in four risk, though we have not enough figures yet. Again, this is obviously useful in early diagnosis. A nice piece of work by a general practitioner recently concerned one of these families with Hirschsprung's disease. The index patient was a boy who had an operation at the hospital for such children and died about 15 years ago. A sister is now grown up. Her first boy had long-segment Hirschsprung's disease and died at another hospital. The next boy was normal. I had told the general practitioner that with this family history there was about a one in six risk for any further child, irrespective of sex. Next time when he sent her into the obstetric hospital he sent a note to this effect. The obstetric registrar asked what he should do about this, and was told that if the child had not passed meconium within 24 hours he had better be sent into hospital. He rang me up after 12 hours and said that no meconium had been passed and he thought the intestine was obstructed; that child had a rectal biopsy done and Hirschsprung's disease was proved 18 hours after birth, which I think is the world's record and a credit to the general practitioner concerned.

The future

We realize that we are only at the start of genetic counselling and that it is going to be developed greatly. In all the common conditions, which are of mixed genetic and environmental aetiology, there is reasonable hope that if one can pick out those genetically at risk and can find out what are the additional environmental

triggers required, one can not only make an early diagnosis but also prevent the condition developing at all. In looking for environmental factors one has to realize that there are only certain families at risk. The place to look for environmental factors which act as a trigger, for example to the development of hare-lip, is in familes where there is already a genetic risk, as in families where father and one child have already been born affected. This will lead to a new kind of public health, prophylaxis of disease through knowledge of particular genetic predispositions in individual families, rather than the kind of mass public health measures applied to whole populations which have been so successful in the past. Probably only the family doctor can apply these new techniques and I see preventive medicine in the next 50 years increasingly going back into the hands of the doctor who knows his individual families.

DISCUSSION

Question: What are the teratogenic potentialities of methylthiouracial?

Dr Woollam: The drug can be used to produce malformations in animals, and it can also be used to sensitize animals to the effect of vitamin A. I do not pay much attention to the effect of a drug on animal pregnancy as an indication of what is likely to happen in human pregnancy. I know of no recorded case of a human malformation attributed to methylthiouracil, although it has been in use for a fairly long time and quite a number of cases must have fallen within the age group in which pregnancy is likely. I should consider it like other drugs which produce malformations in animals, such as penicillin, streptomycin, and insulin, as probably not having the same effect in the human.

Chairman: As a corollary, I suppose it is right to recall that apart from a teratogenic effect, methylthiouracil may have an effect on the foetal thyroid, particularly in late pregnancy, but that is a different matter altogether.

Question: What genetic counselling is given to epileptics?

Dr Carter: Obviously the first thing is to try to find the cause of the epilepsy. If it is due, say, to epiloia (tuberous sclerosis), then it is