MEDICAL PRACTICE

Contemporary Themes

Hereditary Disease and Its Control*

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Today when accidents and malignant disease are being tackled with some success increasing interest is being shown in hereditary disease—that is, disease which may be passed from parents to children through reproductive cells.

Tay-Sachs Disease

Waren Tay was born in 1843; he qualified in medicine at the London Hospital and was appointed to it as a surgeon. He was also on the staff of the Royal London Ophthalmic Hospital at Moorfields and City Road, and the North East Hospital for Children, which became Queen Elizabeth Hospital, Hackney Road. A versatile man, he was also dermatologist to the Hospital for Diseases of the Skin. In 1881 he reported his findings in the eyes of a 1-year-old child with severe muscular weakness. Six years later, in 1887, Bernard Sachs gave a detailed clinical and pathological account of the disease and gave the name “cherry red spot” to the macular changes. He recognized that the condition was hereditary and occurred in Jewish babies and called it amaurotic family idiocy. He was born in Baltimore in 1858 to German immigrant parents and after studying at Harvard and Strasburg he became a leading neurologist in New York, and in 1905 wrote the first American book on paediatric neurology. He lived on into the penicillin era and died in 1944.

Tay-Sachs disease is characteristically commoner among

Ashkenazi Jews than among Sephardic or any other Jews. It must have originated after, perhaps long after, the diaspora which followed the conquest of Jerusalem by Titus during the first century A.D. Historical evidence shows that Jews in east Europe did not often marry with gentile neighbours or members of other Jewish communities but remained isolated. In such a Tay-Sachs community the affected babies would die but the carriers would survive, and if they had a slight selective advantage in fertility they would increase in numbers. Myrianthopoulos and Aronson² suggest that this is the case, and that some immunity to tuberculosis is a possibility and an important one in crowded mediaeval towns.

It was calculated from the incidence of cases that 1 in 30 Ashkenazis would be carriers, compared with 1 in 300 in other populations. Now that carriers can be identified by blood tests the figures for the Ashkenazis have changed to, for example, 1 in 23 in Baltimore, Washington, and London and as high as 1 in 14 in Toronto. Presumably the Baltic Jews who went to Toronto included many who came from one particular region with a high carrier rate and were not much diluted by immigrants from other places.

This instance of the relationship between a hereditary disease and a group of people stands out because of its rather homogeneous nature, but the disease is not limited to Jews. The disease and its cause, deficient enzyme hexosaminidase A, seem to be the same in Jews and non-Jews.

Mental defect due to phenylketonuria (P.K.U.) is uncommon in Jews; it is commoner in Celts in Ireland and west Scotland. Saugstad³ has shown that P.K.U. patients in Norway as a group do not have the pattern of blood groups characteristic of Norwegians but a pattern characteristic of the Irish and Scots; she says that Scots immigrated to Norway 1000 years ago and they brought the P.K.U. inheritance. P.K.U. is also common in Poles; did some of the migrating Scots move up the Baltic? It would be interesting to find out the blood groups of P.K.U. Poles and compare them with the usual distribution in Poland. Dr. C. O. Carter, having calculated mutation rate and the effects of inheritance, thinks that the relevant migration may have occurred earlier, not long after the ice age ended in Norway.

*Based on the Tay-Sachs Foundation Lecture delivered at the Institute of Child Health on 2 December 1974.

Some Blood Diseases

Several common hereditary diseases affect the blood. Sickle-cell anaemia is widespread across tropical Africa and it travelled with the slave trade from west Africa to the West Indies and the United States; there, about one in 600 Negroes have it and suffer from the lethargy of anaemia and the pains produced by blood clotting in the bones, lungs, etc. Each patient has parents who are carriers of the condition but who are usually healthy; they comprise 7-9% of the Black population of the United States¹—4 000 000 carriers. To guess at the total number affected by the disease itself is difficult; it is probably about 300 000. These patients are to be pitied but the carriers in Africa are compensated. Their red blood cells have too short a life for full development of the malaria parasite so small children do not so often die from malaria. Thus, the sickle trait is preserved and has become common, but it has no survival value in non-malarial countries.

Mediterranean anaemia is another common condition due to an abnormal haemoglobin which is also thought to help infants to withstand malignant malaria. It is found from Spain to Cathay, and though there are two diseases chemically— α - and β -thalassaemia—the effects of each on the patient are the same. The wide distribution must be due to at least two original mutations and probably more.

An acute destruction of blood had long been known to occur in certain Mediterranean people especially southern Italians and Greeks, after eating broad beans (fava beans, hence the name favism). It is said that some Sicilians cannot walk across a field of beans in flower without sickening. In 1942 Dr. W. N. Mann noticed that among Indian troops some soldiers developed anaemia when given mepacrine to prevent malaria. Another antimalarial drug produced anaemia in American negroes. In such drug-induced anaemias the sufferers were Negro, Mediterranean, Indian, or south-east Asian. Men were much more and more often susceptible than women. Blood films showed the presence of Heinz bodies and a connection was suspected. The red blood cells were weakened by the lack of enough reduced glutathione, which was due to lack of the enzyme glucose 6-phosphate dehydrogenase.

Control

In many cases we can do little or nothing to prevent or cure hereditary disease, but we are not altogether powerless and there are such measures as selective breeding, treatment of the mother before the child is born, termination of pregnancy when the fetus is thought to be affected, and treatment of the patient.

Various questions are being asked⁴: should pregnancy be continued when it is known the child will be defective? How defective is too defective? What limits of abnormality can be tolerated and by whom? Should persons who carry genetic defects be allowed to reproduce? To these a well-respected professor of paediatrics adds, "We must somehow find substitutes for natural selection."⁵

BREEDING

Forbidden Marriages

The laws of incest might have been designed to prevent disease but they seem to have been a comparatively late idea. In 1621 Burton wrote in *Anatomy of Melancholy*, "The church and commonwealth have conspired to avoid hereditary diseases, forbidding such marriages as are in any whit allied." Huth as late as 1881⁶ gave many examples of the excellent results of marrying within the family, especially in ruling families where the individuals could be seen to be superior to their subjects. This seems naive because children of rulers are fortunate in many material ways besides the genes they inherit, but Huth's point was that the marriage of near kin did not necessarily have bad results. Inter-marriage is common in aristocratic families. In

limited experience of children's ailments in six ruling families I have seen definite ill effects in only one and a suspiciously large number of miscellaneous congenital abnormalities in another.

Is incest harmful? Adams and Neel⁷ found that about 20 children of incestuous unions were born each year in Michigan and that those born to brother and sister turned out quite well but that father-daughter unions carried a great risk of early death or of major congenital abnormality. Obviously the causes may be more social than genetic, which may be the reason why Carter⁸ found the results of brother-sister incest just as disastrous as father-daughter union in Britain, nearly half the children being mentally retarded or dying young of congenital disease.

Infanticide

Australian Aborigines, Bushmen, American Indians, and Samoyeds killed deformed babies⁹ but infanticide is not an efficient method of control as it does not touch the carriers. Sterilization of patients has rarely been carried out but may have a future. For example, Huntington's chorea usually has its onset after the child-bearing age has begun, and it is such a terrible disease, dominantly transmitted, that anyone who knew he would get it might wish to be sterilized.¹⁰ Whether it is ethical to tell anyone in apparent good health that he will die demented, epileptic, and paralysed is a pressing question.¹¹

Screening for Carriers

The diagnosis of carriers of hereditary disease with a view to preventing two of them marrying has much to commend it in countries where marriages are arranged. These are becoming fewer as a young man's fancy lightly turns to thoughts of love without concern for genes. In Italy a register of thalassaemia carriers is being built up to try to prevent marriages between them.¹²

SCREENING

Screening is concerned with looking for cases of hitherto undiagnosed illness, liability to illness, or liability to have children with inherited disease. It is a serious pursuit and, furthermore, it should be beneficial. Before proposing a survey one should ask oneself what one has to offer the people who are discovered to have an abnormality. For example, is it worth diagnosing a disease which has not yet shown itself in baby brothers of patients with Erb-Duchenne muscular dystrophy, when it is untreatable? Yet it can easily be done by estimating creatine phosphokinase.

Who Benefits?

Firstly, the person to benefit may be the patient himself—such as the baby who is found to have phenylketonuria. So successful has this screening become that it is possible for the director of the Phenylketonuria Register to state, "For children born in the U.K. the risk of mental retardation arising from phenylketonuria has been virtually eliminated."¹³ But success brings its own problems. Girls rescued from imbecility in this way must go back to the boring diet if they become pregnant, otherwise their babies may be mentally retarded or epileptic or both. All their children will also be carriers, so the gene pool will very slowly increase. This should not worry us. Penrose¹⁴ pointed out that the "bad" genes might sometimes have compensating advantages: in Africa heterozygote sickle cell infants have a reduced chance of getting cerebral malaria.¹⁵ Now Fuller and Shuman¹⁶ have found unusually high intelligence quotients (I.Q.) in non-carrier siblings of P.K.U. patients. They think that P.K.U. heterozygotes have a metabolic abnormality to overcome so that

if they have merely ordinary I.Q. genes they are at a disadvantage in the battle of life. They require high I.Q. genes, and this shows up in the high intelligence of the metabolically normal brothers and sisters. Nevertheless, there is a heterozygote disadvantage which should lead to reduction in gene frequency.

Secondly, other possible beneficiaries are parents who carry recessive genes for terrible diseases. In most conditions heterozygotes cannot be recognized with certainty. It is not enough for them as a group to be statistically significantly different from non-carriers; there must be no overlap, or at least rare overlap, between the extremes of the two groups, though possibly the public may learn to cope with varying odds as it becomes more mathematically sophisticated. A good example of helping people as parents is the detection of carriers of Tay-Sachs disease. The difference in measurements between carriers and non-carriers may be small but in a good laboratory it is reliable. Kaback in his first survey of over 5000 people, which included 249 carriers, was eventually left with only four cases in which he could not decide whether the individuals were carriers or not.¹⁷ In a marriage in which both partners are carriers they may decide to have no children, to adopt, or to ask for diagnosis during pregnancy with a view to its termination if the fetus is affected.

Thirdly, the beneficiary may be the community. If the patient benefits the community also benefits as it does not have to support a severely handicapped patient, but examples are more obvious outside the field of metabolism, as in the detection of diphtheria or typhoid carriers in closed communities.

Finally, screening may benefit the investigator and his associates. This may be little more than scientific curiosity and so must not be undertaken if there is any risk to the patient. But when blood or urine is being examined anyway there is no harm in carrying out extra tests provided that getting a positive result does not imply a duty to tell the individual about it. Suppose, for example, you found by chance that a 20-year-old man was deficient in hexosaminidase A would you feel that you ought to tell him so that he could exercise discretion in the choice of girl friends? In general if screening is done people should know this, want it, and if possible understand it. One volunteer for Tay-Sachs screening wanted to help our programme but stipulated that he should not be told the result. Probably wrongly, his offer was accepted, but fortunately the result was negative.

When a condition is known to occur specially often in a particular group of people an attempt may be made to screen that group. Tay-Sachs disease in Ashkenazis is an example. This type of public health activity was pioneered by Michael Kaback in Baltimore and Washington, where, it was calculated, the annual cost of screening was covered if it led to two patients fewer needing prolonged hospital care. The government of the Province of Quebec pays the whole cost of the programme in Montreal, for the same reason. These programmes are at best partial successes. Much depends on publicity and also on social homogeneity.

TREATMENT OF THE MOTHER

Prevention of disease where there is a hereditary set-up to produce it is brilliantly exemplified by the work of Clarke *et al.*¹⁸ Severe jaundice of the newborn is produced by a mother's antibodies acting on her baby before birth and destroying his or her blood. By injecting Rh antibodies into the mother shortly after delivery the baby's blood cells can be destroyed before they have time to induce her to produce antibody. Even if the mother has already developed antibodies from an earlier pregnancy or blood transfusion a later pregnancy can be made safe by plasmapheresis—replacing her dangerous blood plasma by someone else's.¹⁸

FAMILY LIMITATION

Limiting the number of children reduces births to older parents

more than to younger parents. This in itself contributes to reduction in mongolism and hydrocephalus.¹⁴

PRENATAL DIAGNOSIS AND ABORTION

Where two parents have had a child affected by a disease which is recessively inherited the risk of affection of a later born child is one in four. Provided the condition can be diagnosed with near certainty during the first four months of pregnancy it is right to offer parents amniocentesis at 15 weeks (when there is enough liquor amnii) which allows time for cell culture and diagnosis, and if this is positive, abortion. At 20 weeks and thereafter abortion is less safe (and also less acceptable if the mother has been quickened by fetal movements). Amniotic puncture seems remarkably safe in experienced hands provided that ultrasound is used to locate (and avoid damaging) the placenta. This technique is reliable in Tay-Sachs and Pompe's diseases, while in some laboratories it may reasonably be used in the Hunter, Hurler, and Lesch-Nyhan syndromes, and in metachromatic leucodystrophy, cystinosis, galactosaemia, methylmalonic acidemia, and maple syrup urine disease.

Apart from these recessively inherited diseases there are other conditions in which amniocentesis is justifiable. Neural tube defects (spina bifida and anencephaly) may recur in a family. These conditions permit excretion of α -fetoprotein into the fluid. If it is found abortion is justified. As methods improve tests will probably be done on maternal blood instead of liquor amnii and can then be performed in all and not just "high risk" pregnancies.

Yet another field for study is in the chromosomes. A mother over 40 years old has a one in 50 to one in 100 chance of bearing a mongol with an extra chromosome, and the chances are higher with translocation of part of a chromosome—with a D/G translocation one in 10 to one in 20.

Though it is not possible to diagnose haemophilia or Duchenne muscular dystrophy by amniocentesis the sex of the fetus can be discovered. Ordinarily both these conditions occur in males and abortion may be performed. Terminating all male pregnancies in affected families will sometimes kill unaffected fetuses and this may be unacceptable to some people, but not, I imagine, to parents who have already watched, helpless, the progressive paralysis of muscular dystrophy in one of their children.

Treatment

In some cases all that may be required to treat a hereditary disease may be the correction of a physical defect such as a cleft palate. Similarly, we may use medicines such as cholestyramine or clofibrate in hypercholesterolaemia. Another obvious way of avoiding trouble is to withhold the extrinsic factor, such as a drug, from the patient who is susceptible to it.

So far we have mentioned conventional treatment, but there is much excitement over newer methods. The diseases we are considering originate in the cell, and may be attacked by replacing the substance which the cell cannot make, either because it lacks the wherewithal or because manufacture is prevented by a blocking or inhibitory gene.

Brady *et al.*¹⁹ gave intravenous infusions of the specific enzyme to patients with Fabry's disease. The enzyme was obtained from human placenta but they found that fresh plasma or white blood cells with platelets were equally effective. Patients with this disease are candidates for kidney transplantation for they die of renal failure. It is important to know whether an organ graft can be a form of treatment for a metabolic disease. Probably in Fabry's disease it can²⁰ though some doubt remains about what Desnick describes as "metabolic engineering."²¹

A patient dying of Gaucher's disease was given a spleen graft.

Though its was finally rejected it seemed to have had some metabolic effect.²²

Infusions of plasma or white blood cells into patients with mucopolysaccharide storage disorders have been found to clear some of the excess accumulation²³ and even to have produced clinical improvement, though it does not always work.²⁴

One of the most promising novelties is the invention of liposomes, which are little spheres composed of alternating layers of lipids and water within which soluble substances—proteins, including enzymes, or drugs—can be trapped. They are made of physiological materials—for example, cholesterol—can be broken down by cells, do not leak, and their contents can be washed off their surface. Injected intravenously they are removed from the blood within minutes and taken up by the liver and spleen, where they enter the cell and get into the lysosomes in usable form.²⁵ This has happy implications for the treatment of storage diseases and, if drugs and immunoglobulins are usable, perhaps for cancer too.

Brady suggested in 1966²⁶ that we might one day be able to control inborn errors of metabolism by feeding in the required messenger RNA or DNA, and that day seems nearer now. It has not yet been done with liposomes but attempts have been made with viruses; a bacteriophage (the λ -phage of *Escherichia coli*) carries the gene which is missing in galactosaemia. In fibroblast culture of cells from a patient with this disease the phage was shown to provide the enzyme and prolong the life of the cells.²⁷ The Shope virus causes papillomata in rabbits but it also carries arginase, the enzyme which is missing in argininaemia, and the living virus has been injected into two children in the hope of terminating this disease,²⁸ presumably unsuccessfully as no more has been heard of it. Such a treatment if successful would be one stage further on than injecting the enzyme, being really a graft at intracellular level.

It would be a brave new world that had such creatures in it.

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Nurse Therapists in Behavioural Psychotherapy

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Summary

Five registered mental nurses (R.M.N.s) were trained over two years to become behavioural psychotherapists for adult neurotic disorders. They achieved results comparable to those obtained with similar patients and methods by psychologists and psychiatrists. Similar results were maintained when over a third year the therapists were seconded to work in four hospitals and a general practice. Patients were satisfied at being treated by nurses. After initial teething difficulties nurse therapists became valuable members of treatment teams during both training and secondment, becoming accepted

by most nurses, psychologists, and psychiatrists with whom they came into contact. The training of further nurse therapists would facilitate treatment of many disabled neurotics who would otherwise go without effective treatment. Training nurse therapists takes less time and money than training psychologists and psychiatrists because less of their education is redundant to the skills involved. The pool of R.M.N.s suitable for training is much larger than that of psychiatrists and psychologists. The nurse therapists can be integrated relatively easily into treatment teams. The present nursing structure imposes restrictions on the advancement of clinical nurse specialists and a clinical tree is badly needed parallel with present administrative and teaching hierarchies. An 18-month course in adult behavioural psychotherapy has been recognized by the Joint Board of Clinical Nursing Studies for England and Wales so that nurse therapists seem destined to be a lasting feature of future treatment teams.

Introduction

"Doctors are beginning to realize that responsibility which has traditionally been in their domain can be delegated safely to others" commented a recent editorial in the *British Medical Journal*.¹ Such realization applies to not only obstetrics, dental care, and paediatrics but also psychiatry. One sign of it is the

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