



## Active management in Serious Genetic Disorders

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### Abstract

Twenty years ago we were taught to classify the cause of any medical condition into those that were 'genetic' and those that were 'acquired'. Subsequently the acquired group could be subdivided according to aetiology. Either directly or by implication we were told that genetic disorders were untreatable and that they were always rare, making up an insignificant proportion of medical practice. This article gives a personal view of the field of medical genetics and is based on two established facts, firstly that genetic diseases are now so frequent that every doctor should be conversant with basic genetic principles. Secondly many genetic conditions if not amenable to curative treatment, are at least responsive to careful management which can prolong and increase the quality of life. At this stage we should emphasise one other aspect, which concerns the philosophy behind genetic counselling. Such counselling is not just the calculation of empiric or theoretical risks that a disease will recur, followed by telling the family and then leaving them to come to terms with unpleasant probabilities. In genetic counselling the range of options open to different members of a family can be fully explained in the light of their risks. At the same time counselling of a wider nature can be offered providing emotional support to many members of the family. By allowing individuals within a family to come to terms with the emotional aspects of an inherited condition, counselling, not necessarily provided by a genetic counsellor alone can be actively therapeutic. Let us now select some severe disorders with a major genetic component and examine the therapeutic approaches available.

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# PRINCIPLES AND PRACTICE ACTIVE MANAGEMENT IN SERIOUS GENETIC DISORDERS

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*"... et nous faisons maintenant la medicine d'une methode toute nouvelle"*  
Le Misanthrope, Moliere, 1666

Twenty years ago we were taught to classify the cause of any medical condition into those that were 'genetic' and those that were 'acquired'. Subsequently the acquired group could be subdivided according to aetiology. Either directly or by implication we were told that genetic disorders were untreatable and that they were always rare, making up an insignificant proportion of medical practice. This article gives a personal view of the field of medical genetics and is based on two established facts, firstly that genetic diseases are now so frequent that every doctor should be conversant with basic genetic principles. Secondly many genetic conditions if not amenable to curative treatment, are at least responsive to careful management which can prolong and increase the quality of life. At this stage we should emphasise one other aspect, which concerns the philosophy behind genetic counselling. Such counselling is not just the calculation of empiric or theoretical risks that a disease will recur, followed by telling the family and then leaving them to come to terms with unpleasant probabilities. In genetic counselling the range of options open to different members of a family can be fully explained in the light of their risks. At the same time counselling of a wider nature can be offered providing emotional support to many members of the family. By allowing individuals within a family to come to terms with the emotional aspects of an inherited condition, counselling, not necessarily provided by a genetic counsellor alone can be actively therapeutic.

Let us now select some severe disorders with a major genetic component and examine the therapeutic approaches available.

## **DOWN'S SYNDROME**

In the United Kingdom there are at least 19,000 patients with this chromosomal disorder, of whom around 30% are in long-stay institutions. It is well known that the older pregnant woman has a higher risk of having a Down's baby, so that above the age of 40 the risk exceeds 2%. It is less frequently understood that over 70% of babies with Down's syndrome are born to mothers who are aged less than 35, simply because the majority of pregnancies occur in younger women. The first implication of this figure is that amniocentesis, followed by selective termination of pregnancy, if offered to women over 35 will make only a small reduction in the birth incidence of Down's syndrome. At present there are no screening tests available to identify most of the younger women at risk of having babies with Down's syndrome. Since amniocentesis for the detection of chromosome abnormalities cannot be offered to all pregnant women, it follows that for the foreseeable future there will continue to be a large number of Down's births. Therefore it is essential to pursue all possible approaches in treatment.

## **Management**

Virtually all babies with Down's syndrome are identifiable at birth and this presents the

advantage of early initiation of active management. This begins with a frank discussion with both parents, hopefully with the baby present, in which the features are explained briefly as well as what is known of the aetiology. Initially the parents may be so shocked that they say very little and appear to have no appropriate questions. However, it is important that they can form a good relationship with *one* doctor so that they can ask about whatever might worry them during the succeeding weeks or months. In the first few days it is often useful to suggest that the couple meet other parents, from similar families. This not only provides emotional help from someone who has met (and overcome) the same distress, but another parent can also encourage the couple to talk openly with the professionals about their fears and uncertainties. It is essential that all who confront a couple in this situation give honest answers to all their questions, even if the answer is that we do not know. Only in this way can a trust be built up with the professional services which is strong enough to augment active management.

The mainstay of management of most aspects of Down's syndrome in the first year is active stimulation. Thus the hypotonia is helped by simple physiotherapy whilst social development is aided by active stimulation of visual, auditory and tactile senses. In all aspects the parents and siblings can play a major role here, with appropriate professional guidance. A most successful recent innovation has been the appointment of educational home visitors who guide the parents and encourage them to teach a wide range of skills. The preliminary results of such 'active' management are yet to be evaluated fully but the signs are that the prognosis in Down's syndrome has been improved to such an extent that information in many textbooks, printed only a few years ago, is now out of date and excessively pessimistic.



**Figure 1:** Close contact with normal children is a further and most successful way to ensure that Down's infants are stimulated. A normal child can be much more sensitive to the short attention span of a handicapped child than an adult can.

For the immediate future there are still more possibilities. Firstly we could consider the impact of the electronics industry on the habilitation methods available for Down's syndrome infants. There are a variety of electronic toys which are now sold for normal children which provide stimulation for certain useful skills. I have already found that children with Down's syndrome can enjoy these games and can thereby be encouraged to develop some quite specific skills (eg. memory or hand-eye coordination). Within a short time simple computer systems, dedicated to the minimisation of mental handicap will improve communication skills and thereby encourage better integration in the community. Some doctors are quite unaware of the recent rapid advances in educational psychology which have led to improved, more pragmatic teaching for the mentally handicapped. In Down's syndrome their excessive pessimism rapidly influences the parents who may either abandon all attempts to teach the baby simple skills (a course of action which would "handicap" the normal infant) or else may lose faith in all professionals, having realised the inaccuracy of early medical advice.

## **Vision and Hearing in Down's Syndrome**

There are several surveys which show that up to 80% of young children with Down's syndrome have visual or hearing handicaps which are easily amenable to treatment. In the case of hearing difficulty there are several causes, but transient or partial deafness often results from the narrower external auditory canal which, along with the susceptibility to upper respiratory infection, leads to middle-ear damage. It is easy to understand why a young child who is transiently deaf, who has visual handicap and whose parents have been told that the prognosis for speech and other communication skills is very poor, will fail to achieve.

Down's syndrome is certainly a genetic condition which at present is incurable but there are surely numerous possibilities for active management. The principle to use in management is that the condition has many features, affecting a wide range of body functions. Only when we have treated all the treatable aspects fully will we truly discover the extent of the genetic handicap and the influence of new measures upon the developing Down's child's brain. When I counsel the parents of a Down's baby and they ask about the future I do not give them an unqualified and optimistic prognosis. Rather I tell them what we do now know while also mentioning all the positive actions that can be taken and that are known to minimise handicap.

## **INBORN ERRORS OF METABOLISM**

Although individually very rare (the incidence of phenylketonuria is around 1 in 10,000 while for maple syrup urine disease it is 1 in 120,000) the inborn errors of metabolism collectively cause sufficient handicap for every paediatric unit to be provided with resources for diagnosis and management. For over 20 years phenylketonuria (PKU) has been successfully managed by restriction of dietary phenylalanine. It has also been shown that the dietary regime can be relaxed in late childhood without apparent deterioration in cerebral function. Thus this genetic disorder can be managed so that the major handicap is preventable even if the genetic defect persists. There are other inborn errors in which this principle could be applied such as maple syrup urine disease in which restriction of the branched-chain amino acids (leucine, isoleucine and valine) can lead to immed-

iate clinical improvements. In this disease also, therapy with pharmacological doses of thiamine (up to 1000 mg per day) which acts with residual enzyme as a co-factor can also produce both clinical and biochemical improvement. Recent experience with PKU has highlighted what may be a problem in many genetic diseases. Women who have been successfully treated for PKU in infancy and childhood are now reaching the child-bearing ages and several pregnancies have now been described in the literature. The risk of their offspring also having PKU is low, provided the father is unrelated to the mother and therefore unlikely to be a carrier of the disease. However, if the mother does not return to the special PKU diet before the time of conception and throughout pregnancy, the foetus will be subjected to grossly elevated levels of phenylalanine and is at high risk of congenital defect, particularly mental handicap. Institution of a phenylalanine controlled diet prior to and throughout pregnancy can almost completely prevent such disasters. Whilst this highlights a growing problem, the PKU experience illustrates how other inborn errors of metabolism may affect a foetus and opens up new approaches to preventive therapy.

Still more exciting is the possibility that some important inborn errors might be permanently controlled by the replacement of a missing enzyme with grafted tissue, possibly fibroblasts or bone marrow stem cells, from a histocompatible donor. Early evidence shows that in certain types of mucopolysaccharidosis, particularly Hurler's syndrome, such therapy can lead to prolonged biochemical improvements. The long-term clinical benefits are not yet known but, in theory at least, a bone marrow graft will be able to establish a source of monocytes from which macrophages in all parts of the body including the brain can be derived. Such treatment might be considered for many inborn errors of metabolism provided the enzyme is synthesised by monocytes or other donated cells.

## **CYSTIC FIBROSIS**

Cystic fibrosis (CF) is the most frequent autosomal recessive condition in Caucasians with a birth incidence of approximately 1 in 2,000. This means that around 1 in 22 are carriers of the disorder, a proportion which has stimulated a

search for precise methods for identifying the abnormal gene, whether in single or double dose. In Edinburgh, Drs. Jean Manson and David Brock have produced an antibody in guinea pigs to cystic fibrosis protein which shows early promise in detecting carriers of CF or pre-clinical cases. However, despite intensive research throughout the world the exact cause of CF remains elusive.

Our failure to know the biological basis for cystic fibrosis, however, need not mean that there is no treatment. Around 80% of CF patients have pancreatic insufficiency and for most of these malabsorption symptoms are improved adequately after regular therapy with appropriate enzymic dietary supplements. It may not be long before 'human' pancreatic enzymes are produced inexpensively in pure forms by bacteria as a result of genetic hybridisation manipulations.

All CF patients are at risk of respiratory infection and this is the major cause of morbidity and mortality from the disease. During the past 20 years, however, antibiotic therapy and active physiotherapy have brought about a fair improvement both in the quality of life and in life expectancy, so that over 50% of CF children can now survive into adulthood. It is clear that there is a long way to go before the CF problem has been controlled, but some new regimes, which aim at individualising therapy for each patient based on the respiratory and immunological competence, are producing promising results.

#### **CONGENITAL CNS MALFORMATIONS: A RAPID GENETIC SOLUTION?**

When I began genetic counselling almost ten years ago we saw many couples who had recently lost a baby in the neonatal period because of spina bifida or anencephaly. We knew that the risk of further children being involved was moderately high, 1 chance in 20, or even higher if other children had been affected or there were previous spontaneous abortions. At that stage the mainstay of prevention was the parents' decision to have no further children. Shortly afterwards, in 1972, Dr. David Brock and Roger Sutcliffe showed that the amniotic fluid level of alpha-fetoprotein (AFP) was markedly elevated in pregnancies in which there was an open neural tube defect. This added a new approach for the prevention of CNS malformations. Parents at high risk could be offered

an amniocentesis and, if the foetus was thereby shown to be affected, they could consider a termination of pregnancy. However, the (small) risk of amniocentesis was only justified if there was a high risk of neural tube defect, recognised because of a previous affected baby. Two or three years later David Brock found that a high proportion of pregnant women whose foetus was affected could be identified by the measurement of *maternal serum levels* of AFP at 16 weeks gestation, followed by selective amniocentesis in the 2 or 3% whose level was above a certain point. This identified the *first* foetus to be affected in many families.

During the past 18 months it has been shown that multivitamin or folic acid therapy taken for two months before and after conception may significantly reduce the risk of neural tube defect, even in 'high risk' families. The reason for this beneficial effect is far from clear but the data point to a simple dietary approach to the control of common and serious malformation syndromes. In the space of ten years we have passed from the dilemma of families with a high recurrence risk, via the ethical difficulties of selective terminations of pregnancy, towards realistic evidence of primary preventive therapy.

#### **SUMMARY**

This article has described briefly some aspects of four diseases or groups of diseases which are genetically determined in whole or in part. Collectively they account for morbidity in around 1% of all conceptions and this fact belies the notion that genetic diseases are rare, even though there are many other inherited disorders which have not yet been considered. The main aim of this review has been to emphasise positive methods of management in four quite different situations. However, the principles of management are the same in all instances: if a direct cure of the pathological process is not yet possible then the different aspects of the pathology can be tackled, separately and energetically, such as deafness due to infection in an infant with Down's syndrome or the respiratory infections in cystic fibrosis. Such simple measures can very greatly improve the quality of life and the prognosis notwithstanding our lack of knowledge about the precise genetic defect. Furthermore, the possibility of

direct therapy which is curative may not be far off for several genetic disorders. Anyone who seeks to manage a disorder with a hereditary element in the 1980s would do well to take note of Hilaire Belloc's sarcasm:

"Physicians of the utmost fame  
were called at once, but when they came  
they answered, as they took their fees,  
'There is no cure for this disease'."

There may be few 'cures' for genetic diseases but for the physicians with a therapeutic interest there is a challenge which may often be successfully tackled.

