*A handbook of*

# CLINICAL GENETICS

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# A Handbook of Clinical Genetics

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# *Preface*

This text was originally planned for nurses but when completed was also considered to be suitable for medical students and doctors needing an introduction to clinical genetics. There are many more detailed books on the subject available. Most of the clinical material and pedigrees illustrated have been obtained from the counselling service and we are very grateful to all those patients, consultands and families who have attended over the years. We are also grateful to those health visitors and doctors, in particular Dr J. I. McLachlan MB, DCH, DRCOG, who have contributed to the service since its commencement.

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J. S. Fitzsimmons
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# 1 Introduction

During the past decade doctors and nurses have become aware of the increasing interest in clinical genetics and the growing demand for genetic counselling. This has been the case in most specialities and has benefited the management of many patient problems. For example, paediatric nurses now accept genetic counselling for the families of handicapped children as a helpful and much needed service. The midwife and obstetric staff involved in the expanding field of prenatal diagnosis are already reducing the number of children born with serious abnormalities. In the community the health visitor and the primary health care team dealing with a wide variety of medical and surgical problems recognise the hereditary aspects of many diseases. Finally nursing staff in psychiatric or general medical wards will have to deal with the serious consequences of disorders such as Huntington's Chorea with its familial implications. In all these areas therefore it is possible to appreciate the increasing importance of genetics in everyday nursing and medical practice. It is necessary now to look at why some of these changes have come about. The following factors appear to be important.

## Changes in Morbidity and Mortality

There have been significant changes in the causes of morbidity and mortality in childhood over the past half-century. As a result of immunisation children no longer die, or very rarely so, from diseases such as poliomyelitis or diphtheria. Antibiotics have helped to prevent deaths from other infections, and ante-natal care has improved the chances of babies surviving the process of birth. Today death in early infancy and childhood is more likely to be the result of a serious congenital abnormality and although we have no evidence that the number of such abnormalities is increasing they have been highlighted by the reduction in deaths from other causes. In 1975 congenital abnormalities accounted for almost 25 per cent of all stillbirths, 20 per cent of deaths in the first week of life and one in

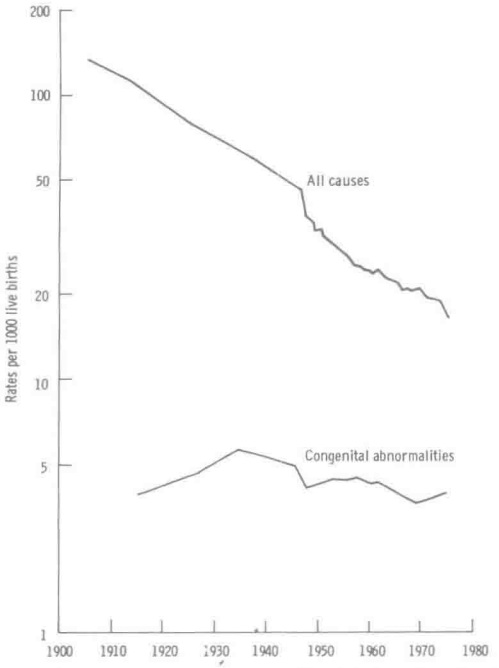



**Fig. 1.1** Infant mortality per 1000 live births. Deaths from all causes including congenital abnormalities. England and Wales (After Birth Impairments OHE)

four deaths in the first year of life. Although the infant mortality rate has progressively decreased, the number of deaths from congenital abnormalities has shown little change.

If we now examine the various types of serious congenital abnormalities (Table 1.1), at the top of the list is that group of conditions referred to as neural tube defects and comprising spina bifida, meningomyelocele, anencephaly and some cases of hydrocephalus. The list also includes Down's Syndrome or mongolism and takes account of serious handicapping conditions such as mental retardation, deafness and blindness. By totalling the incidence of these various disorders it can be seen that approximately 25 children per thousand births will suffer from one or more of these serious problems. This is equivalent to 2.5/100 or, more practically, a risk of 1 in 40 of a serious abnormality in any pregnancy. This figure comes as a surprise to many couples and for that reason it is important to put it into perspective. It does also imply a 39 to 1 chance that a child will not have a serious congenital abnormality.

| | Approximate Incidence / 1,000 births |
|---|---|
| Neural Tube Defects | 3 - 7 |
| Congenital Heart Disease | 6 |
| Severe Mental Retardation | 4 |
| Downs Syndrome | 1.5 |
| Cleft Lip / Palate | 1.5 |
| Talipes | 1 - 2 |
| Cerebral Palsy | 3 |
| Blindness | 0.2 |
| Deafness | 0.8 |
| Abnormalities of Limbs | 1 - 2 |
| Others including Renal Tract Anomalies | 2 |
| | 25 - 30 |

Table 1.1 Incidence of serious congenital abnormalities per 1000 births.

Events are now moving so rapidly that as a result of prenatal diagnosis neural tube abnormalities are becoming less commonly the cause of neo-natal or childhood death. It is now congenital heart disease and kidney abnormalities which are the major causes of death in this period.

There have also been demonstrable changes in mortality and morbidity in adults. Improved social circumstances and antibiotics have helped prevent deaths from conditions such as tuberculosis and other infections. Coronary artery disease, various types of cancer and degenerative disease are now the major problems. In some of these conditions, for example some types of coronary artery disease, the genetic component may be clearly recognised. In others, such as diabetes, hypertension and mental illness, it is more difficult to evaluate the contribution of genetic factors. Nevertheless, genetic disease does provide a considerable addition to the total burden of human illness. Although it is difficult to assess this accurately it has been estimated that if we combine adults and children then about 1 in 10 individuals will have serious genetic disease. Another 1 in 50 will have disease of unknown aetiology probably, to some extent, related to genetic factors.

## Fall in Birth Rate

In 1977 there were approximately 600 000 infants born in England and Wales and this is the lowest annual delivery rate since records were introduced. For the first time our population was in negative

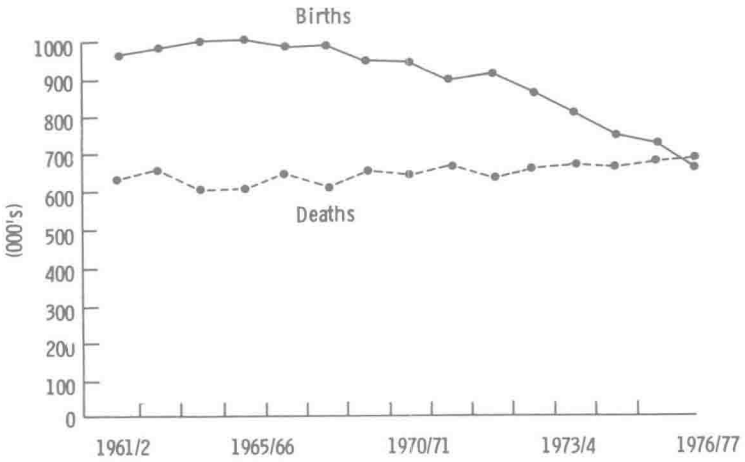



**Fig. 1.2** Birth rate and death rate. England and Wales (After Population Trends HMSO)

balance; deaths from all causes outnumbering births. There has been a predicted rise in the birth rate during 1978–1979 due to an increase in the number of women entering the childbearing years. This was the result of the 'baby boom' of the 1960 period but there is no evidence to suggest that it reflects any long term trend.

As a consequence of the fall in the birth rate the average number of children per family has decreased and it is important to note that this trend is not a new one. Records from 1850 show that the decrease has been a steady one and in 1977 the average number of children per family in this country was two or slightly less than two.

Parents rightly wish their children to be born healthy and able to enjoy a normal, active life. Because each child is now more likely to be the result of a planned pregnancy this desire is more often expressed. Fifty years ago with larger families it was not unusual for a child to be born with a serious handicap. Today, such an occurrence is more likely to be seen as preventable and many young couples appear to seek some means of guaranteeing that their children are born healthy and stay that way. Another consequence of fewer pregnancies is that a miscarriage is now a much more significant event and couples may be referred to genetic counselling clinics for advice about some aspects of this problem. As with other conditions it is only possible to give sensible advice if the cause of the miscarriage or stillbirth can be established. It is important therefore to obtain more detailed post-mortem examination of aborted fetuses and stillborn babies.

## Advances in Technology and Treatment

Changing patterns of disease in our community have influenced thinking on medical research and practice. There is now more emphasis on the preventative aspects of medicine and health education. However, the prevention of conditions such as Down's Syndrome and spina bifida have had to wait for advances in technology which have become available over this past few years. Increasing experience with amniocentesis and the advent of ultrasound have made prenatal diagnosis possible and safer. In addition there have been significant advances in *cytogenetics*, i.e. the study of chromosomes and their abnormalities. An important landmark in the development of this science was the finding of an extra chromosome in patients with Down's Syndrome. Subsequently changes in the number and structure of chromosomes were demonstrated in other disease states. All of these changes may be identified in a preparation of chromosomes referred to as a *karyotype* and shown in Fig. 1.3.

In the past few years it has been confirmed that there is an increased level of a fetal protein, alpha-fetoprotein, in the amniotic fluid surrounding a fetus with spina bifida or anencephaly. This has made it possible to offer prenatal diagnosis and selective abortion to couples at risk of having a child with this serious abnormality. A

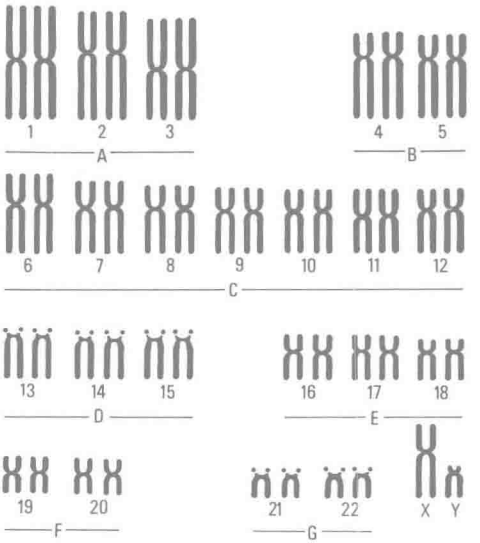



**Fig. 1.3** Normal unbanded karyotype. The chromosomes are numbered and grouped according to size. Sex chromosomes bottom right. This is a male.

similar approach is now adopted in a number of rare serious diseases such as the mucopolysaccharidoses. These may result in mental retardation in addition to physical abnormalities.

More recently it has become possible to identify fetal blood vessels with the aid of an instrument called a fetoscope. This enables the examiner to sample fetal blood and to make a diagnosis of some genetic diseases, e.g. Duchenne muscular dystrophy and thalassaemia. There is still a fairly high risk associated with this procedure but refinements in the technique and the instruments used are likely to make it safer and more common in the future. Increasing experience with ultrasound should help in the diagnosis of fetal renal cystic disease and possibly also in the detection of abnormalities of head-growth such as microcephaly or hydrocephalus.

Another major stimulus to interest in genetic disease came with the demonstration that children born with phenylketonuria could develop normally, provided they were commenced on a suitable diet in the newborn period. In this recessively inherited disease affected children have a deficiency of an enzyme and cannot metabolise the phenylalanine present in a normal diet. As a consequence of this they may be mentally retarded. This biochemical disease is not yet preventable but like other diseases has now been shown to be treatable. Research may well show that other genetic diseases may be treatable in the same way.

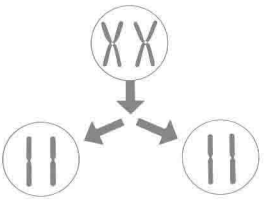
## Complex Social Changes

In recent times the liberalisation of the laws on abortion and improved techniques of contraception have, in addition to reducing the birth rate, obviously allowed women much more freedom than was possible in the past. This has meant their involvement in professions and other jobs which would have been denied them had they to care for children. The burden of caring for a handicapped child is usually more the responsibility of mother than father. It is understandable, therefore, that many women today would wish to avoid such restrictions on their freedom.

In addition to changes in the law there have been some more subtle changes. Today, there is less pressure from parents on young couples to have children. There is also less pressure from society and an only child is not considered to be such a tragedy as was the case in the past. Many couples today elect not to have any children, and one of the reasons given for this is the increasing cost of rearing a child in times of 'inflation'. Politicians and the media frequently suggest that all of us have higher expectations. It is difficult to define exactly what this means but undoubtedly the need for individual fulfilment is now

more frequently discussed than was the case a generation ago. There is an increasing demand for more leisure time and an acceptance that this applies to women as well as men. The divorce rate has increased and marriage is no longer considered the necessary consequence of two people wanting to live together.

Over the years there has been a steady increase in demand by the public for more information about disease and its consequences. It is difficult to be sure of the real reasons for this but the media, particularly television, appear to have played a large part in stimulating the public to question medical opinion. This, in many cases, has meant that doctors and nurses have to spend more time discussing patient problems. It would seem reasonable that parents of a seriously handicapped child would want to know why this had happened and would also want to know the chances of it happening again. Assessing the recurrence risk of an abnormality and attempting to answer the questions raised is a large part of the rapidly growing field of *genetic counselling*. This new addition to standard medical practice seems to have resulted from all the factors so far discussed, coupled with the demand of our patients for more information. We will see, however, that it is not sufficient to compute a risk for a particular condition; it is also the responsibility of the genetic nurse and doctor to ensure that this information is understood and is imparted in a sympathetic manner.



# 2 Genetic and Environmental Factors in Disease

Having outlined some of the reasons for the increasing interest in genetic counselling it is necessary to identify those disorders in which this type of advice and information is relevant.

Reference has already been made to the large number of children born every year with a serious congenital abnormality. In many cases the cause of the abnormality is not apparent but in others, specific causative factors can be identified. These may be divided into two major groups – genetic and environmental. Today, the study of congenital anomalies and their causes, the science of *teratology*, is an expanding field. There is a constant search for those agents, *teratogens*, which produce abnormalities of growth or formation of organs in the fetus.

## Environmental Factors

Infection with rubella in the first trimester of pregnancy is known to be the cause of a number of serious abnormalities in the fetus including mental retardation, cataracts and deafness. Other infecting organisms which can produce fetal damage are cytomegalovirus and the protozoon responsible for toxoplasmosis. Both may produce hydrocephalus and mental retardation. Some drugs administered to mother in the early stages of pregnancy have been shown to be the cause of a small number of abnormalities, about 5 per cent of the total. Thalidomide is the most quoted example but this drug is no longer in use and we must now examine other commonly used drugs for possible ill effects. Steroids are known to cause changes in the

genitalia of female infants; the anti-convulsant, Epanutin, may be related to hare-lip abnormalities and oestrogens contained in the 'pill' if taken in early pregnancy may possibly produce ill effects. More recently it has been recognised that excessive intake of alcohol by mother may cause intellectual retardation and some minor physical anomalies in her infant. Some antimetabolites have also been shown to be teratogenic. It is obvious we have managed to identify only very few environmental factors causing congenital abnormalities.

## Genetic Factors

In other infants it is apparent that an inherited factor has been largely responsible for the condition and the transmission of the disease from mother or father to their offspring may be very obvious. A good example is Marfan's Syndrome in which one or other parent has long thin fingers and toes (arachnodactyly). In addition such patients are at increased risk of rupture of the aorta and many have dislocation of the lens. Each child born to such a parent has a high risk of inheriting the abnormal gene which causes the condition. In this situation it is genetic factors and not the environment which is producing the teratogenic effect. This is not to suggest that genes work in isolation. A person's ultimate physical development is the result of the interaction between genetic inheritance, the intrauterine environment and subsequent postuterine environment. This is an important basic principle of genetics, and nature (genes) and nurture (environment) cannot easily be separated. Nevertheless, there are a considerable number of diseases in which an hereditary factor or genetic effect is more important and such diseases are referred to as *single gene* or *unifactorial* disorders. Examples are tuberose sclerosis, achondroplasia, haemophilia and muscular dystrophy. In some of these the disease is clearly transmitted from generation to generation, whereas in others the hereditary background is only recognised when more than one affected child is born to normal parents. Another group of conditions, usually without a familial background but nevertheless due to disordered gene function, result from chromosomal abnormalities. Whereas genes, normal or abnormal, cannot be seen by any current means, it is possible to demonstrate abnormalities of chromosomes by examining a karyotype. This may reveal alterations in either their number or their structure. One of the most common examples of a chromosomal abnormality is Down's Syndrome or mongolism. In this disease there is an additional chromosome and this can be shown to be an extra No. 21. Normally there are only two of each numbered pair

but in Down's Syndrome there are three of pair 21. This is referred to as *trisomy 21*.

The total number of patients born with chromosomal abnormalities is small, probably only about 1 per cent of live births. However, it has been shown by examination of material from early miscarriages that a considerable proportion, probably as high as 30 per cent, of aborted fetuses have some form of chromosomal abnormality. In some this is due to the loss of chromosomal material, e.g. Turner's Syndrome, in which there is only one X chromosome instead of the usual two. In others the total number of chromosomes may be doubled or trebled, a condition referred to as *polyploidy*. The placenta from such fetuses may be larger than usual and this may give a clue to the underlying cause. In single gene defects it is an alteration in the quality of gene action which seems to be the important factor. In chromosomal disorders with many genes involved the clinical abnormalities are the result of quantitative changes.

There are other diseases which may afflict members of a family more often than could be accounted for by chance. In these it is assumed that there is a genetic factor which produces a predisposition to the disease, but some additional environmental agent is also necessary for its production. These are referred to as *multifactorial* diseases and the genetic component is thought to be the result of a combination of numerous genes, i.e. a polygenic effect. Unfortunately, this group contains many common diseases such as spina bifida, club feet and some form of heart disease. In addition it also includes major health problems affecting adults such as diabetes and probably schizophrenia.

In some conditions twin studies may be useful in deciding the relative importance of genetic or environmental factors. Twins are of two kinds, identical or *monozygotic* and non-identical or *dizygotic*. Identical twins have the same genetic constitution because they result from the division of a single fertilised ovum. Non-identical twins are no more alike than ordinary brothers and sisters. Diseases due entirely to genetic factors should affect both identical twins. They are said to be *concordant*. Diseases due to environmental factors should normally not affect either monozygotic or dizygotic twins more often than singleton births. In this situation they are said to be *discordant*. When both environmental and genetic factors are at work the degree of concordance will reflect the genetic contribution; a high concordance rate suggesting that heredity is more important than the environment.

Finally, a number of **developmental defects** without any obvious cause, may be shown in future to be at least partly the result of genetic action. A great deal of further research is necessary to eluci-

date the many possible factors that may disturb normal growth and development of the human embryo.

Despite the increasing number of diseases now recognised to be of genetic origin there are considerable difficulties in assessing accurately the part played by hereditary factors in the overall burden of human illness. As we have seen, in some disorders the genetic component may be very obvious. Hereditary diseases affecting successive generations in a family have been recognised for many centuries and are recorded in the earliest medical literature. In other disorders, however, where the genetic contribution may be less obvious or where the disease does not produce clinical manifestations until later in life, the hereditary aspects may be easily overlooked. This is even more likely today with small families and with the increasing tendency for families to disperse more widely than was the case in the past. In some villages and rural areas however it may still be possible to observe hereditary factors at work. For this reason the community nurse and general practitioner may be able to anticipate specific diseases because of their knowledge of particular families. There are now between 1000 and 2000 disorders known to be the result of faulty gene action and many more in which genes may play a major role. Some surveys of the prevalence of genetic diseases in the community have been reported but much more detailed information is required. In the 1960s a survey from Northern Ireland suggested that 26 per cent of the occupants of all institutional beds, 6 per cent of all consultations with general practitioners and 8 per cent of those with hospital consultants, were patients suffering from genetically determined disease. More recently in England and North America it has been reported that as many as 30 per cent of all paediatric admissions to children's units are the result of genetic or congenital disease. A recent study of an American adult medical unit revealed that approximately 13 per cent of the patients had illnesses resulting from hereditary factors.

There is little doubt, therefore, that genetic disease is a major cause of death and chronic ill health. In order to plan health services for the future it is essential to have information about the incidence of such diseases and their distribution in various regions and populations. There is an obvious need to monitor accurately serious birth defects and to detect early any changes in the frequency or pattern of malformations. Unfortunately there is an increasing number of drugs prescribed to women in the first trimester of pregnancy when the fetus is at maximum risk. Some of these drugs may be teratogenic and thalidomide is a good example. Following its introduction to the British market it was frequently used in the management of vomiting in early pregnancy. Despite sporadic reports of its possible role in the

production of limb abnormalities in the fetus, a large number of infants were affected before it was eventually withdrawn from use.

More recently it has been reported that the anticoagulant, Warfarin, may be teratogenic and the infant in Fig. 2.1 demonstrates the abnormalities which may be seen. There is shortening of the limbs, a depressed nasal bridge and an odd-looking face. The patient has a congenital heart lesion and cataracts. The most characteristic finding however is stippled calcification at the growing ends of the long bones. This combination of abnormalities is referred to as Conradi's Syndrome. In common with some other conditions it may result from either environmental or, on occasions, genetic factors. Although rare it has occurred in more than one child in some families suggesting recessive inheritance. In others, as mentioned, it has been reported following the ingestion of Warfarin by mother early in pregnancy. A disease which results from an environmental agent but which is very similar to that resulting from genetic factors is called a *phenocopy*. It is interesting also that disease resulting from genetic

**Fig. 2.1** Conradi's Disease. Striking physical appearance. May be caused by genetic or environmental factors.