I

Developmental Problems Before, During and After Birth

The Prenatal Period

Chapter 1 begins with a description of the major genetic disorders, chosen to illustrate conditions, each of which has a major impact on (*inter alia*) intellectual, physical, behavioural or sexual development. Nature plays an early 'role' in the primary prevention of severe disorders. Very many concepti are either genetically abnormal and thus fail to develop, or they implant themselves in a location incapable of sustaining them, and consequently the pregnant mother-to-be miscarries. The prevention of inherited disorders by means of advice from genetic counsellors, the use of screening methods (ranging from amniocentesis to gene tests), and the decision to terminate a pregnancy, are discussed. Ethical and moral issues with regard to termination – at the personal and policy levels – are raised as a subject of concern. The many gaps in our knowledge about genetic mechanisms in the causation of disabilities await further research on the human genome, and its underlying protein activity.

The Uterine Period

The first task of the newly conceived baby-to-be is to survive a potentially hazardous prenatal journey, and make the transmission from a watery existence of parasitic dependence on the mother's body, to a healthy, physiologically independent life in the outside world. In spite of all the risks described above, the vast majority of neonates are in a healthy state. Fortunately, the mother's womb is almost always a hospitable environment in which the baby-to-be can develop.

In relatively atypical circumstances there are psychological and physical influences which disrupt the development of the tenant by disturbing the host mother, notably during embryonic development. Appendix V contains a brief summary of prenatal stages of development.

Much of the evidence on the precise effects of maternal stress on her unborn child is extremely difficult to evaluate. It is clearly difficult to infer cause–effect relationships from the only possible ethical evidence – retrospective correlational studies. In addition, observations to do with the effects of prenatal influences on postnatal developments in the child are contaminated by the mother's management of her baby after birth, and by other environmental and genetic factors that cannot be controlled. Despite these difficulties and caveats there are findings of interest to suggest that home visiting and other forms of physical and emotional support can be beneficial to young mothers, and these are discussed briefly in Chapter 2 (a longer account awaits later chapters).

The term *teratogen* is applied to any disease, chemical, drug, or other environmental agent capable of harming a developing embryo by causing severely retarded growth, physical deformities, deafness, blindness, brain damage, and also death. I have chosen to describe the effects of two major potential teratogens – excessive smoking and alcohol ingestion during pregnancy – because of their near universality, and the high risk of serious damage to which they can subject the developing fetus.

The chapter ends with a diagnostic and treatment profile of two congenital disorders: fetal alcohol syndrome and hydrocephalus.

■ The Perinatal and Neonatal Periods

Chapter 3 introduces the subjects of problematic births and the diagnostic and treatment profiles in several congenital conditions. It also investigates the risks of being a very low birth weight baby, problems involving brain injury and other disabilities. Maternal stress during pregnancy, family poverty and social disadvantage are among the multiple causes (along with infections) to produce preterm labour and low birth weight babies (e.g. Pattenden, Delk and Vrijheid, 1999). Early interventions for babies at high risk are described. The chapter describes a 'window of opportunity' in which to apply these methods (e.g. home visiting, intensive care and early stimulation) in order to mitigate short- and long-term ill-effects.

CHAPTER 1

The Prenatal Period

Genetic Disorders and Disabilities

The phenotypes that result from genetic disorders tend to be expressed in various ways (Fryers, 1984). Not all of the genetic disorders lead primarily to intellectual disabilities as is the case with the Fragile X syndrome. In some, the major impact is behavioural (e.g. Tourette's syndrome); in some the main impact is physical and medical (e.g. cystic fibrosis); in others the genetic fault leads to anomalous sexual development (as in Klinefelter's syndrome). There follows below an account of several disorders (a small sample of the many hundreds of inherited conditions) chosen *inter alia* to illustrate their particular consequences for (i) intellectual; (ii) physical; (iii) behavioural; and (iv) sexual development.

Impact on Intellectual Development

Fragile X Syndrome

Diagnostic history

Fragile X syndrome, also referred to as the Martin–Bell syndrome, seen in approximately one in 1,200 males and one in 2,500 females, is the next most common form of genetic intellectual disability (mental retardation) after Down's syndrome. Males with the syndrome are usually intellectually disabled and tend to exhibit characteristic behaviour patterns and physical features (Hagerman, Amery and Kronister, 1991; Hagerman and Silverman, 1991). Affected females display a similar, but generally less extreme phenotype.

The disorder had probably been present for many centuries but its first identification had to await the 1960s. This was followed, after a period of clinical

'silence', by the discovery in the late 1970s of the link between an abnormal fragile site on the X chromosome and a syndrome of intellectual disability. The next major breakthrough was the identification in 1991 of the gene which causes Fragile X (FMR1). Once the Fragile X syndrome was recognized as a distinct condition, cases began to be diagnosed in all races, world-wide.

Diagnosis

The phenotypic manifestations of Fragile X syndrome as described in the literature are not specific, and the list of associated difficulties can lead to problems of differential diagnosis. Approximately 15 to 20 per cent of those with the disorder exhibit autistic-like behaviours: difficulty in relating to people, poor eye contact, hand-flapping or odd gesture movements, hand-biting, and poor sensory skills.

Individuals with Fragile X syndrome often share a number of recognizable physical features, including:

- a high arched palate
- strabismus (lazy eye)
- large ears
- long face: coarsening of features
- macro-orchidism (large testicles) in the post-pubertal male
- hypotonia: poor muscle tone
- generalized disorder of connective tissues
- flat feet
- sometimes increased head circumference.

Clinical features

Although many individuals with Fragile X syndrome have a characteristic 'look' (long face and large ears), by no means do all have the other so-called 'typical physical features'. There is such variability in their extent (with some intellectually disabled males showing few of the physical components) that clinical diagnosis becomes difficult.

Many hospitals and laboratories perform blood tests to diagnose Fragile X syndrome. To confirm the diagnosis it is necessary to detect an alteration in the FMR1 gene (chromosomal locus Xq27.3). Changes in FMR are detected by molecular genetic testing. DNA studies have improved the accuracy of testing (usually carried out on a blood sample) for Fragile X syndrome. The tests will reliably diagnose those whose learning disabilities are caused by the disease, and identify carriers of the syndrome.

Developmental features

Fragile X syndrome is more common in males (approximately one in 1,500) than females (one in 2,500). Affected individuals have normal growth and stature, and no associated malformations. Males typically have a moderate to severe form of intellectual disability. Females may also be affected but generally have a mild form of impairment.

Behaviour problems and speech/language delay are common but variable features. The boys tend to be impulsive, over-active, easily distracted, and inattentive. Girls have similar difficulties concentrating. They tend to be extremely shy and socially withdrawn.

Causation

In the 1990s, as we saw earlier, the Fragile X gene (FMR1) was identified and found to contain an 'in tandem' repeated trinucleotide sequence (COG) near its 5' end (see Warren and Nelson, 1994). The mutation responsible for Fragile X syndrome involves expansion of this repeat segment. The normal number of CGG repeats in the FMR1 genes varies from 6 to around 50. The larger the size of a mother's premutation, the greater the risk of expansion to a full mutation in her offspring. More than 99 per cent of affected individuals have a full mutation. Males and females carrying a premutation gene are unaffected.

Male carriers are referred to as 'normal transmitting males' and they pass on the mutation, relatively unchanged in size, to all of their daughters. These daughters are unaffected, but are at risk of having children who are affected. Most, but not all, males with a full mutation are intellectually disabled and show the typical characteristics of Fragile X symptoms. Approximately one-third of females with a full mutation, are of normal intelligence; one-third are of borderline intelligence, and one-third are intellectually impaired.

Treatment

There is no specific treatment for Fragile X syndrome. Instead, effort is directed toward training and education to help affected children reach as high a level of functioning as possible. Behaviour therapy and/or mild medications are used for behaviour problems, as well as speech therapy for speech and language and sensory difficulties.

Children need to be diagnosed as early as possible so that an appropriate intervention can be planned. As families generally learn about the existence of genetic faults in their family background when their children manifest the syndrome, the

issue of timing for access to genetic counselling and screening is vital. To assess this matter of timing, a survey was conducted in 2001 of 140 parents whose first child affected by the syndrome, was born and had the condition diagnosed between 1990 and 1999 (Frank Porter Graham Child Development Institute, University of North Carolina at Chapel Hill). This report indicated that approximately half of the families did not receive the diagnosis for more than a year after their first concerns about their child's development or behaviour. Half reported having subsequent pregnancies before the syndrome was diagnosed in their first child. These results underline the need for screening facilities and an early diagnosis.

Prevention

- *Genetic counselling*. Genetic counselling is provided by a professional geneticist as a means of learning about the inheritable nature of Fragile X syndrome, and the risks to future offspring, or to other relatives who may be unwitting carriers of the syndrome. To this end, families with a history of Fragile X syndrome are likely to be advised to seek genetic testing and recurrence risk counselling.
- *Screening*. Prenatal testing of a fetus is possible following a positive carrier test in the mother, by means of molecular genetic testing. When the mother is a known carrier, DNA testing can determine whether the fetus inherited the normal or mutant FMR1 gene. Chorionic villus sampling (CVS), although a standard technique for prenatal diagnosis, may still require a follow-up amniocentesis if it is necessary to resolve an ambiguous result. Detained discussion of prevention procedures is continued toward the end of the chapter.

Impact on Physical Development

Cystic Fibrosis

Diagnosis

Cystic fibrosis (CF) is almost always diagnosed during infancy or early childhood. It is an example of a condition in which aberrant genes cause serious life-long physical problems. The severity of this disease ranges from mild bronchial symptoms and male sterility to severe lung, pancreatic, and intestinal difficulties. Suspicion is likely to be aroused where there is a high incidence of the condition in

relatives. A simple blood test can detect many, but not all of the genetic abnormalities (there are several hundred) that cause CF.

Clinical features

CF does not follow the same pattern in all patients but affects different people in different ways and to varying degrees. However, the basic problem is the same: an abnormality in the gland which produces or secretes sweat and mucus. Sweat cools the body; mucus lubricates the respiratory, digestive, and reproductive systems, and prevents tissues from drying out, protecting them from infection.

- Children with CF lose excessive amounts of salt when they sweat. This can disturb the balance of minerals in the blood, possibly causing abnormal heart rhythms. Going into shock is a risk.
- Mucus in CF patients is very thick and accumulates in the intestines and lungs. The result is malnutrition, poor growth, frequent respiratory infections, breathing difficulties, and eventually permanent lung damage.
- Lung disease is the usual cause of death in most individuals with CF.

Comorbid conditions

CF can cause various other medical problems. These include:

- abdominal pain and discomfort;
- enlargement of the right side of the heart;
- gassiness (too much gas in the intestine);
- rectal prolapse (protrusion of the rectum through the anus);
- sinusitis (inflammation of the nasal sinuses);
- nasal polyps (fleshy growths inside the nose);
- clubbing (rounding and enlargement of fingers and toes);
- pneumothorax (rupture of lung tissue and trapping of air between the lung and the chest wall);
- hemoptysis (coughing of blood).

Causation

Symptoms of CF only appear if a child has two copies of the abnormal gene that cause the disease, one from the mother and one from the father. The faulty genetic make-up affects the way chloride ions are transported across cell membranes. This

combines with an increase in sodium absorption to cause excessive mucous secretion in the lungs and digestive tract, increasing the risk of infections.

If a child has only one abnormal gene then he or she is a 'carrier' – one asymptomatic person in 25 carries the CF gene. Carriers are unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed. Thus, children of parents who have no symptoms can still have CF, but only if both parents contribute the abnormal gene to their baby. If both partners actually carry the cystic fibrosis genes, the risk of their baby having cystic fibrosis is 1 in 4 (25 per cent).

Treatment

Since CF is a genetic disease, the only way to prevent or cure it would be with gene therapy at an early age. Ideally, gene therapy could repair or replace the defective gene. Knowledge of a gene mutation alone, however, does not provide sufficient information for clinicians attempting to plan an intervention. Their first task is to understand the normal function of the gene or genes associated with particular diseases, and then determine how that function is disrupted by the mutation. The need is not only for more fundamental and clinical research, but also for the resolution of the many complex moral issues that arise from altering the basic genetic 'instructions' of individual's future lives.

An option for treatment would in theory be to give a person with CF the active form of the protein product that is scarce or missing. At present, however, neither gene therapy nor any other kind of treatment exists for the basic causes of cystic fibrosis, although several drug-based approaches are being investigated. The best that clinicians can do currently is to ease the symptoms of CF and retard the progress of the disease, so the child's quality of life is maximized. This is achieved by the use of antibiotics combined with physical strategies to clear the thick mucus from the lungs.

Therapy is tailored to the needs of each patient. CF was inevitably fatal in childhood, in the past. More effective methods of treatment developed over the past two decades have increased the average lifespan of CF patients to nearly 30 years. For patients whose disease is very advanced, lung transplantation may be an option.

Prevention

As CF is an inherited condition affecting approximately one in every 2,500 babies, prenatal testing of the fetus by means of amniocentesis, is likely to be recommended by a genetic counsellor in the light of a family history (see below).

The fluid surrounding the fetus is obtained through a needle. It contains some of the baby's cells that can then be tested for the CF genes.

The likelihood that a test will accurately identify an abnormal gene depends, in part, on the ethnic background of the person being tested. CF tests currently identify 90 per cent of CF mutations in Caucasians, 50 per cent in African Americans and Hispanics, and 30 per cent in Asian Americans.

The perinatal screening of CF babies is a controversial matter because of (*inter alia*) the stigma attached to the large numbers of children who appear to be developing normally. This is a physical disease that places a great burden on the child, and on parents who have to attend to an unending and onerous task of pulmonary care. Support for the family is crucial in protecting the emotional development of children with CF, and the morale of their parents.

Impact on Behaviour

Gilles de la Tourette's Syndrome

The disorder is named after Georges Gilles de la Tourette, the pioneering French neurologist who first described an 86-year-old French noblewoman, the Marquise de Dampierre, with the condition in 1825. In 1885, he reported nine cases of what came to be named Tourette's syndrome (GTS) in which the triad of multiple tics, caprolalia (swearing) and echolalia were present (see Robertson, 2004).

Diagnosis

GTS is an inherited neurological disorder characterized by repeated involuntary movements and uncontrollable vocal sounds called tics. They have to occur multiple times per day. Sometimes, the syndrome will result in the vocalization of inappropriate words and phrases. In a few cases, such tics can include obscene words and phrases. The symptoms of GTS generally appear before individuals are in their late teens. Tics must be present for at least one year. Although the symptoms range from very mild to quite severe, the majority of cases fall into the mild category. The natural course of GTS varies from child to child, adult to adult.

Clinical features

GTS is diagnosed by observing the symptoms and evaluating the family history. Which may indicate a genetic predisposition to the disorder. The first signs are

usually facial tics, commonly eye blinking. With time, other motor tics may appear, such as head jerking, neck stretching, foot stamping, or body twisting and bending. Caprolalia is the best known of the vocal tics and consists of the involuntary interruption of the flow of the person's speech with various unprovoked obscenities. It is not uncommon for a person with GTS to continuously clear his or her throat, cough, sniff, grunt, shout or bark.

Children and adolescents can sometimes suppress their tics for a brief period, but eventually tension mounts to the point where the tic 'bursts out'. They may tend to touch other people inappropriately and repeat actions obsessively. A few self-harm by head banging and biting their lips and cheeks. Only a relatively small proportion of children suffering from GTS displays either remission or an exacerbation of their tics. Tics worsen in stressful situations and improve when the person relaxes or is absorbed in an activity.

GTS may be associated with:

- obsessive-compulsive symptoms
- learning disorders
- AD/HD
- social difficulties
- poor achievement at school.

Developmental features

The average age of onset of GTS (based on world studies) is around 7 years. The symptoms generally appear before the individual is 18 years old. Individuals can expect to live a normal life span. Although the disorder is generally lifelong and chronic, it is not a degenerative condition; it does not impair intelligence. Tics tend to decrease with age, enabling some patients to discontinue using medication. In a few cases, complete remission occurs after adolescence. Leckman, Zhang and Vitale (1998) suggest that there is evidence that the majority of GTS symptoms disappear in half of the patients by the age of 18 years, given:

- an early age at onset (5.6 years)
- severe tics at around 10.

Although tic symptoms tend to decrease with age, it is possible that psychological disorders such as depression, panic attacks, mood swings, and anti-social behaviours may increase in frequency and/or intensity.

The psychosocial consequences of GTS are quite likely to be self-consciousness, embarrassment, irritability and depression. On the neuro-developmental side of the equation, the children display difficulty with visual-motor and expressive language tests, suggesting a disturbance in intellectual 'performance' processes. Although autism (another neuro-developmental disorder) and GTS are distinct disorders, they share certain behavioural characteristics: obsessive-compulsive behaviours, abnormal motor behaviour, and echolalia.

Epidemiology

People of all ethnic groups are affected by the disorder, males being affected 3 to 4 times more often than females. It is estimated that its prevalence in children is approximately 1 per cent of mainstream schoolchildren between the ages of 6 and 17 years. The prevalence of GTS in children with special educational needs, and also autism, is high (Robertson, 2004).

Causation

Psychodynamic theories have not stood the test of time. Prenatal and perinatal events have been inculpated in the aetiology of GTS (Leckman, Zhang and Vitale 1998), but to date the precise causes continue to be unknown. However, it is generally considered currently, to be a neuro-psychiatric brain disorder which is determined by genetic, environmental, hormonal and other influences (see Cody and Hynde, 1999). Although there is a suggestion that the genetic disorder is transmitted via a single major gene locus with autosomal dominant inheritance, no single gene has yet been identified. As with other genetic conditions interest is being shown in, and research pursued on genome scans (e.g. the Tourette Syndrome Association International Consortium for Genetics, 1999).

Treatment

There is no cure for GTS; however, the condition in many children does tend to improve as they mature. A holistic (i.e. multilevel, multidisciplinary) approach to treatment seems the most favoured intervention (see Robertson, 2004). The majority of children require no medication, but it is available when symptoms interfere with daily functioning.

GTS medications may help to reduce specific symptoms. The treatment of choice is clonodine. This drug has been in use longest, and has enjoyed modest success for the symptoms of agitation, AD/HD, and hyperarousal (see Fonagy, Target, et al., 2002). Neuroleptic and antihypertensive drugs can have worrying long- and short-term side effects, and the use of stimulants is controversial.

Relaxation techniques and biofeedback may be useful in alleviating stress. Behavioural techniques are of limited value. Psycho-education for the children with GTS, their parents and teachers, is a vital resource.

Impact on Sexual Development

Klinefelter's Syndrome (47,XXY)

Klinefelter's syndrome (KS) – a sex chromosome anomaly that causes hypogonadism – was discovered in 1942. Harry Klinefelter and his co-workers at the Massachusetts General Hospital in Boston described nine men who had enlarged breasts, sparse facial and body hair, small testes, and an inability to produce sperm. Researchers discovered by the late 1950s that men with this syndrome had an extra sex chromosome – 47 chromosomes in each cell of their bodies XXY instead of the usual 46, the XY male pattern. In the early 1970s, researchers screened the chromosomes of thousands of newborn infants. The XXY chromosome pattern turned out to be one of the most common genetic abnormalities.

Although the cause of the condition (now referred to as Klinefelter's syndrome) – the extra sex chromosome – is widespread, the symptoms and features of the syndrome that may result from having the extra chromosome are an uncommon occurrence. There are many men who live out their lives never suspecting the additional chromosome in their bodies. For this reason, the term 'XXY male' is used by many clinicians in preference to 'Klinefelter syndrome'.

Diagnosis

KS is diagnosed by a medical history, physical examination, and chromosome analysis. With the increase in testing by amniocentesis or chorionic villus sampling (CVS) KS may be diagnosed prenatally, but also immediately after birth. The infant appears normal at birth, the defect usually only becoming apparent in the pre-teen years (around ages 11 to 12) when males often begin puberty.

Epidemiology

In random surveys, KS is found to appear in 1 in every 500 to 1,000 live born males. The fact that the largest percentage of these males is never diagnosed indicates that in many cases there is an under-diagnosis operating for various reasons, among them the fact that large numbers of affected individuals pursue normal lives with no particular medical or social complications.

Clinical features

The severity of symptoms may vary from one male to another depending on the number of extra X chromosomes and how many cells in the body are affected. Males with more than one extra X chromosome generally have more symptoms. Some males with KS may not fully develop secondary male sexual characteristics – such as the growth of the testicles and penis, deeper voice, and body hair. They are not able to produce enough sperm to father children. Some mild cases may go undetected, with no abnormalities present except infertility. Tall stature and abnormal body proportions (long legs, short trunk) are common.

Developmental features

It has been reported that individuals with KS are predisposed to psychiatric disorders. The combination of feminine physical features, poor motor coordination, and language and memory difficulties is likely to affect self-esteem and contributes to feelings of anxiety and insecurity, especially from adolescence onwards.

As children, they often learn to speak much later than do other children and may have difficulty learning to read and write. And while they eventually do learn to speak and converse normally, the majority tend to have some degree of difficulty with language throughout their lives. The children with KS are frequently reported to have below-average intelligence, a claim not supported by large-scale screening studies. Only about 20 per cent score lower than 90 on standardized intelligence tests. Most children with KS have average to superior intelligence.

Nevertheless, boys with the extra X chromosomes syndrome commonly have learning disabilities and tend to perform poorly in school, even when they have average or above IQs. They often achieve low verbal scores, poor short-term auditory memory, and poor data retrieval skills. The risk of AD/HD is high. In many cases, delayed or diminished speech and language skills or dyslexia add to their difficulties. Fortunately, language disabilities can be treated with speech therapy, the chances for success being greatest if begun in early childhood.

Causation

A person's sex is determined by the X and Y chromosomes. Normally, men have 46 chromosomes, the XY.male combination. The cause of KS is an extra X sex chromosome – 47 chromosomes (XXY) in each cell of their bodies. There are other, less common variations such as 48,XXYY, 48,XXXY, 49,XXXXY, and XY/XXY mosaic. All of these are considered KS variants, and are diagnosed by means of a chromosome analysis (karyotype), carried out usually on a blood sample.

Treatment

Testosterone therapy will improve the development of secondary sexual characteristics. This replacement therapy can have a positive effect on mood and behaviour, improving self-esteem and decreasing fatigue and irritability. Testosterone treatment usually starts at the beginning of puberty. Once this treatment begins, it needs to be continued for life. There is no treatment for the infertility associated KS. Testosterone therapy can increase osteroid formation and bone mineralization, but only if initiated before age 20.

Frequently, adolescent boys with KS undergo breast tissue development which continues to increase in size. This could necessitate its surgical removal. Enlarged breast tissue can be treated with plastic surgery if it is disfiguring.

Management of KS in teenage boys may require help from the school, especially for those boys who have learning difficulties. Counselling may benefit children and adolescents with emotional difficulties due to identity problems, low self-esteem, and in adolescence, sexual dysfunction.

Turner's Syndrome (Bonnevie Ullrich Syndrome; Gonadal Dysgenesis; Monosomy)

Diagnosis

Turner's syndrome (TS) was first described by Henry Turner, at the University of Oklahoma. He reported a set of common physical features in seven of his patients in an article published in 1938. The presence of the damaged or deleted X chromosome which indicates the endocrine disorder TS had to await the discovery, in the late 1950s, of the technology to perform a blood test of the chromosomes called karyotyping.

Clinical features

It should be noted that symptoms may vary widely among those affected with TS. Most affected girls can be recognized and diagnosed in early childhood by the characteristic physical features (e.g. small/short stature and absent or retarded development of secondary sexual characteristics), also health-related problems, which may include:

- reduction or absence of the ovaries;
- absence of menstruation;

- kidney abnormalities;
- abnormalities of the eyes;
- abnormal liver function;
- ear infections;
- hearing deficits;
- under-active thyroid glands;
- heart defects (e.g. coarctation/narrowing of the aorta);
- arthritis;
- skeletal disorders;
- type two diabetes.

The disorder inhibits sexual development at puberty, and causes infertility.

Developmental features

The ovaries do not develop normally because, with only the one X chromosome present in most children with TS, they do not produce adequate amounts of female hormones. The young teenager will not develop the signs of puberty – breasts and menstruation – unless these hormones are provided. Pubic and axillary hair may grow, the uterus and vagina are normal.

The faulty chromosomes do not mean that girls with TS do not have the identity of 'real life' females. A point that may need to be stressed in counselling sessions is the fact that they are girls or women who have a genetic condition that leads to under-developed ovaries and short stature. However, TS does cause physiological and psychological problems which have an impact on the child's development.

The two X chromosome combination (XX) has an influence beyond determining the sex of an individual; it also affects physiological growth and psychological development. For example, some girls may experience learning difficulties, notably with mathematics. Mental retardation is not a feature of Turner's syndrome, despite the claims published in older medical textbooks. Girls are of normal intelligence; however, the characteristic pattern of intellectual functioning involves a verbal 10 that is generally average or above, but a non-verbal IQ that may be considerably lower because of problems visualizing objects in relation to each other. It is advisable, therefore, to arrange for psychological testing if school problems become evident.

Epidemiology

TS is a rare (1 in 2,500 to 3,000 live births) chromosomal disorder of females. Approximately 800 new cases are diagnosed each year in the USA. The

occurrence of the deleted or damaged X chromosome appears to be a random event. Thus, any couple can have a daughter with TS. In addition, the disorder equally affects those of different ethnic backgrounds.

Prevention

There is no known prevention for TS. Although the cause of this inherited disorder is known in a general sense (the result of an error during the division/meiosis of a parent's sex cells), the precise causal mechanisms that put a couple at risk of having a daughter with TS are not known. The means to carry out preventive interventions awaits discovery.

Treatment

Most girls and women are managed by endocrinologists because the most commonly prescribed treatments for TS involve:

- the use of *growth hormone* to improve growth speed and final adult height;
- *estrogen replacement therapy* to promote the sexual development appropriate to puberty. Estrogen therapy is also important for the development and maintenance of bones;
- *thyroid hormones* for some patients.

Clearly, it is important to identify children with TS as early as possible so that treatment can be initiated to promote normal growth and development. If the disorder is not treated in early childhood, the onset of puberty is delayed. Such a delay in sexual development may disrupt a major task of the teenage years – social development – and lead to low self-esteem. The older child (when in her teens) may feel uncertain about what, if anything, to tell her boyfriend. This concern about disclosing her disorder is likely to arise in other situations and with others in her life, at any time.

Discussing this issue with a trusted and supportive person may assist the youngster to cope with these problems. It is very important that the parents and the girl herself are provided with useful information. A good understanding of GTS and its implications, as well as any treatment plan arrived at in partnership with the assessment team, are vital. Psychological treatment – family and child counselling at the different stages of childhood and adolescent development – may be needed, and should prove helpful.

Prevention of Inherited Conditions

Eugenics

The word 'eugenics' (meaning 'good birth') was coined by Sir Francis Galton (1822–1911) in the nineteenth century, but the practice is age-old. This subject is a distasteful one to mention, nevertheless the use of sterilization as policy in the West (and I'm not referring to the grotesque murders of intellectually disabled people in the name of Aryan 'purity') was commonplace until the 1940s and 1950s.

In the USA compulsory sterilization was applied over 30 states (1907–31) to 12,000 so-called 'inferior' or 'imbecilic' people. This policy of sterilization was continued until 1942. By 1930, 68,000 intellectually disabled people were institutionalized as part of a eugenics policy with little or no regard for human dignity and rights. Sterilization continues to take place to this day in legally circumscribed situations. These issues are discussed by Field and Sanchez (1999) and McGaw (2004).

Genetic Counselling

The following discussion is designed to cover the prevention strategies that apply to all of the conditions described above. The health service comes into play in a secondary-level preventive role by applying what are called 'selective' and 'indicated' targeted interventions. There are two procedures available to prevent or detect abnormalities, with the aim of mitigating their adverse consequences.

First, genetic counselling is the profession of specialists (still relatively few in number) from a medical or nursing background who have an advanced training in genetics and personal counselling. The counselling interview is designed to meet would-be parents' needs for individual information and advice (Harper, 1998). Following an initial session, counsellors usually draw a family tree with the help of the prospective parent to gather information about both sides of the family, and identify problems that may be pertinent. Genetic counsellors provide them with:

- factual information about the risks of passing on hereditary conditions;
- options and reasons for screening genetic disease before conception;
- advice about tests conducted (*in utero*) such as ultrasonography, amniocentesis, and fetoscopy, which determine after conception the condition (e.g. identifying genetic defects) of the fetus.

Genetic counselling is not only a technically complex task; it is also a psychologically delicate one. A discussion of the risks and their implications may be necessary:

- if a mother or father has a family history of hereditary disorders;
- if the mother is in an older age-bracket, has had one or more pregnancies terminated; or has previously given birth to a baby who suffers from an abnormality.

Parents often ask the counsellor: 'Dare I try again?', 'Why did it happen to me?', 'Is there something wrong in my or his family … something inherited?' They may blame themselves for their child's disability, and feel relieved to know that there is no need to feel guilty as it was not within their powers (unless they endangered the pregnancy with avoidable teratogens such as excessive alcohol and nicotine), to prevent it happening. The counsellor is also likely to be asked: 'What tests are there, if I try again?' As the level of risk (base rate) varies for different disabling conditions, the diagnosis of a present or past condition should be accurate in order to make informed predictions about likely outcomes. Clearly, genetic diagnosis has progressed from investigating family trees for inheritable weaknesses, to the detection of fetal genetic abnormalities and the existence of carriers in conditions like haemophilia. This is a good example with which to illustrate several of the issues raised by genetic diagnosis.

The decision about whether to continue, or terminate a risky pregnancy may follow a genetic diagnosis. It is now possible to determine the sex of a fetus from a dense, stainable structure (called a 'Barr body' after its discoverer), allowing a pregnant woman with a family history of X-linked diseases such as haemophilia, to choose an abortion if she is bearing a male fetus. This bald statement about 'choosing' to terminate a risky pregnancy does no justice to the painful personal issues that have to be resolved. Such decisions cannot be 'prescribed' for prospective mothers and fathers. However, clear information about the chances of giving birth to a baby son with haemophilia, or some other disorder, may at least add an objective (factual) element to the highly subjective emotional and moral issues that make deciding so difficult.

Termination of a pregnancy

The World Medical Association offers advice to practitioners about the ethical and moral reservations they may have on this, and other contentious subjects. It suggests that physicians who consider contraception, sterilization and abortion to

be in conflict with their values, may choose not to provide these medical services. However, they should not impose their personal principles on prospective parents, but are obliged to alert them when a potential genetic problem is discovered.

Ante-natal Screening

Ultrasound scanning

Throughout pregnancy, tests are available to ensure that both mother and baby are in good health. Ultrasound scanning utilizes sound waves to form a picture of the baby in the womb. It is often used between the 12th and 16th week of the pregnancy to confirm the age of the baby and to determine the presence of twins. In order to detect serious abnormalities scans need to be conducted between about 18 and 20 weeks.

The Advisory Committee on Genetic Testing (ACGT), part of the UK government's Human Genetics Commission, suggested in a consultation document submitted to health authorities across the country, that a large proportion, if not all, pregnant women could be tested to identify their unborn babies at high risk for developing genetic diseases. They would be offered diagnostic ultrasound in order to screen for the likelihood of Down's syndrome (DS). It may also detect other neurological abnormalities such as spina bifida and anencephaly (failure of the brain to develop).

The nuchal translucency ultrasound screening

This test is not diagnostic but indicates the need for further tests. The ultrasound measures the thickness of the fold at the back of the baby's neck. Babies with DS have increased fluid in the fold and a thicker fold.

The AFB blood test

This is a blood test known also as the Bart's double or triple test, which is performed (with no risk to mother or baby) between the 16th and 18th weeks of pregnancy. A small amount of blood from woman's arm is tested to measure three substances: the level of alpha fetoprotein, and two other hormone levels (the unconjugated oestral and the human chorionic gonadotropin). The constituents of the woman's blood are compared with her age. High levels may indicate the presence of a neural tube defect, for example, spina bifida; low levels possibly indicate the presence of DS. Because of uncertainties – possible alternative explanations for high or low levels – other confirmatory tests are required.

Amniocentesis

This test (carried out usually between the 16th and 20th weeks of pregnancy, under local anaesthesia) withdraws a small amount of amniotic fluid surrounding the fetus with a fine needle. The fetal cells and fluid are separated in a centrifuge and the cells are cultured for a variety of tests (e.g. for sex determination and for biochemical and enzymatic investigations). The risk of a miscarriage due to the procedure is around 1 in 100 pregnancies, and is thought too high for routine use. Laboratory tests investigate the presence of DS, Turner's syndrome, Tay–Sachs disease, neural tube defects and other structural abnormalities, also certain sex-linked conditions.

Chorionic villus sampling – CVS

This technique is carried out to diagnose conditions that would not be detectable until approximately 16 weeks of pregnancy by amniocentesis (*not* including spina bifida or neural tube abnormalities). It is not a routine procedure, but highly specialized. A tiny fragment from the edge of the chorionic tissue is withdrawn with a hollow needle, for testing.

Strep B test

Group B streptococcus in pregnant women (between 10 and 30 per cent unknowingly have the organism) is a leading cause of illness and death among newborn babies, something reputedly more common in the USA than the UK. Pregnant women can be screened for Group B Strep, two to four weeks before labour begins. Antibiotics are administered. In the UK midwives tend to act conservatively and without set protocols. They generally adopt a 'wait and see' policy, monitoring baby and mother for symptoms of illness which then lead to antibiotic treatment. In the USA, a prophylactic use of antibiotics for the mother during labour, and the baby at birth, is more common.

Gene Tests

The Human Genome Project has made it possible, in a way that was unavailable a relatively short time ago, for scientists and clinicians to identify genetic faults that contribute to, or cause many diseases. Advances in gene testing have also provided the diagnostic methods and prognostic knowledge that help them select the most appropriate interventions. Gene tests (also called DNA-based tests) have

had, within a relatively short time, a dramatic impact on many people's lives, allowing families to avoid the risk of giving birth to children with devastating disorders. All diseases have some genetic component, whether inherited directly or the outcome of environmental threats to the predisposed body (e.g. from viruses or toxins). Mutation tests often search for only the most common (currently about 70) mutations. Some diseases, it needs to be remembered, occur disproportionately in certain ethnic groups (see Chapter 3), for example:

- *sickle cell anaemia* (in African Americans and Hispanics);
- *cystic fibrosis* (in Caucasians);
- *Tay–Sachs* and *Canavan disease* (in Ashkenazi Jews).

Several thousand diseases are linked to mutations in single genes that are inherited from one or both parents. Most are very rare, accounting for about 3 per cent of all disease in the general population.

Clinical sensitivity

It is critical, given the critical objectives and implications of genetic testing, to consider the clinical sensitivity of specific gene tests: i.e. the proportion of people with particular clinical conditions they successfully detect. For example, reliable gene tests are required for:

- carrier screening;
- prenatal diagnostic testing;
- newborn screening;
- pre-symptomatic testing to predict adult-onset disorders;
- confirming diagnoses of symptomatic individuals;
- forensic identity testing.

Methodology

In gene tests, scientists directly examine a *DNA sample* (obtained from any tissue, including blood) for mutated sequences; they design short pieces of DNA called probes whose sequences are complementary to the mutated sequences. These probes will seek their complement among some three billion base pairs of an individual's genome. If the mutated sequence is present in the patient's genome, the probe will bind to it and indicate the mutation. Genetic tests might also involve microscopic examination of stained or fluorescent chromosomes, as well as biochemical investigations of gene products such as enzymes and other proteins.

Many different genetic mutations can cause the same disease. The discovery of the genetic causation of cystic fibrosis (CF) is a good example of the value of gene testing, as it is now feasible to determine whether a particular pregnancy carries a normal fetus, a carrier, or a fetus with CF.

National Policy

The Advisory Committee on Genetic Testing (ACGT), mentioned earlier, stated at the conclusion of its study, that women found to have an abnormal fetus should be provided with advice on having an abortion, within legal guidelines. It commented that:

> those who undergo prenatal diagnosis have the wish to have a healthy child. Thus, when a fetus is found to have a genetic, chromosomal or structural abnormality, some may, when provided with information on the effects of the abnormality, choose to seek a termination of the pregnancy.

The draft document stresses the importance of consent from the mother, and the need for procedures and their implications to be explained with clarity. Support would have to be provided once a decision is made.

Not surprisingly, anti-abortion campaigners have criticized the suggestion of large-scale testing, asserting that it amounts to a conspiracy to 'filter out' disabled children before they are born, denying their human rights.