Chapter 3: The genetics of deafness

G. R. Fraser

Definition

Except where expressly stated otherwise, deafness should be taken to be synonymous within the context of this chapter with profound hearing impairment in childhood. In general, this may be taken to connote bilateral hearing loss of sufficient severity and of sufficiently early onset to necessitate special or supplementary educational measures for the learning of speech. It should be noted that such hearing loss is not necessarily congenital. Indeed, it is virtually impossible to distinguish between deafness which is congenital and that which is of rapid onset in the first few weeks or months of life.

This definition may be justified both on pragmatic and on biological grounds. The inability to acquire speech by normal methods of education because of hearing loss represents a useful way of identifying that group of children with the conditions which form the subject matter of this chapter and which give rise, in the majority of cases, to this type and degree of hearing loss. About one in 1000 children suffer from severe educational handicap to this extent as a result of deafness and, of these, approximately one-half owe their handicap primarily to hereditary causes. In the other half, the hearing impairment is due primarily due to acquired causes.

Mendelian inheritance and deafness

Autosomal recessive deafness

This is the most common type of Mendelian inheritance of deafness. The autosomes are the 22 pairs of chromosomes which are not sex chromosomes (X, Y). Autosomal recessive deafness is biologically heterogeneous and may be determined by genes at many different sites, or loci, on these chromosomes. In the simplest case, the gene concerned with hearing exists in alternative forms, a normal and an abnormal, which are known as alleles.

In the vast majority of cases, the normally hearing parents of a child with autosomal recessive deafness are both carriers of an abnormal allele at the same locus. They are said to be heterozygous in that they possess two different alleles at the locus in question, one abnormal and the other normal. The presence of the normal allele ensures that they themselves do not suffer from hearing loss. In such a family, each parent has a 50% chance of transmitting the chromosome carrying the abnormal allele to each child. Thus, there is a 25% chance that any child will inherit two abnormal alleles without any compensating normal allele and, as a consequence, be deaf. Such a child is said to be homozygous for the abnormal allele.

Autosomal recessive deafness, therefore, generally occurs within a single sibship and usually is not transmitted from a deaf parent to a child. Because of the tendency of the deaf to marry similarly affected individuals, exceptions to this rule occur in that some unions involve two persons with the same type of autosomal recessive deafness. In such a case, all the offspring will be deaf since they cannot inherit a normal allele from either parent and, like
their parents, will be homozygous for the abnormal allele. This is a very rare situation because there are so many different causes of profound childhood deafness that each cause individually is of low frequency in the deaf population. Even when the two parents suffer from autosomal recessive deafness which is determined at different gene loci, the offspring will hear normally in that they will inherit a normal as well as an abnormal allele at each locus and will be doubly heterozygous.

A person with autosomal recessive deafness may occasionally marry a heterozygote at that locus who hears normally, or who may be deaf due to an entirely distinct cause. In such a case, each child will inherit the abnormal allele from the first parent and have a 50% chance of inheriting the same abnormal allele from the other parent. The chance of deafness occurring in a homozygous abnormal child of such a union is therefore 50%. This type of family also occurs very uncommonly since the abnormal alleles concerned are individually very rare and the frequency in the population of heterozygotes for even the most common of them is not substantially more than 1%.

A characteristic finding relating to autosomal recessive inheritance of rare conditions such as deafness, is an increased frequency of consanguineous marriages, usually involving first cousins, among the parents of affected children, as compared with the general population. This happens because the alleles concerned are rare and, therefore, a relative of a heterozygote is far more likely to carry the same abnormal allele, inherited from a common ancestor, than is an unrelated marriage pattern.

Because the chance of any child of a marriage between heterozygotes being deaf is only 25% and because of the small family size which is now the rule in economically advanced countries, autosomal recessive deafness most frequently occurs in a single individual who represents an isolated case within the sibship and within the family. It is very important to make every effort to identify the cause of the deafness in such an isolated case since, if autosomal recessive inheritance is operative, a risk of 25% exists for recurrence in subsequent offspring. Occasionally this will be revealed by the fact that the parents are related. More often, clinical findings associated with the deafness will serve to identify a syndrome known to be inherited in an autosomal recessive manner.

The Pendred syndrome (deafness with goitre)

Perhaps the most common autosomal recessive syndrome involving deafness, in European populations at least, is that first described by Pendred in 1896 as an association of deaf-mutism with goitre. Deaf-mutism is of course no longer used as a term to describe this group of children since it has been realized that the difficulty in learning speech is secondary to the hearing impairment.

Brain (1927) first invoked the hypothesis of autosomal recessive inheritance in this syndrome. Furthermore, he clearly foresaw the later discoveries by Morgans and Trotter (1958), that the goitre in this condition is due to an inborn error of thyroid hormone synthesis, and he showed great perspicacity in suggesting that it represented only one of several such errors which could exist. Morgans and Trotter (1958) showed that this defect consists of a partial block in the enzymatic step involving the incorporation of inorganic iodide into organic form in the thyroid gland. Compensatory hyperplasia of the thyroid gland, often leading to
a large goitre, may overcome the deficiency in thyroid hormone synthesis and affected individuals often remain euthyroid throughout life. In the past, surgical removal of the goitre often led to hypothyroidism. This unsatisfactory treatment has been superseded by the administration of exogenous thyroid hormone immediately after diagnosis, which maintains euthyroid status even without compensatory hyperplasia of the gland and, indeed, may lead to a regression in size of a gland which is already hyperplastic. Such treatment has no effect on the hearing impairment.

A specific test of thyroid function can be employed to make an unequivocal diagnosis of the Pendred syndrome in a deaf child with thyroid enlargement. The test is too complex to be used as a routine screening procedure among deaf children without clinical enlargement of the gland, who may be presymptomatic cases of the Pendred syndrome. The test depends on the phenomenon that inorganic iodide contained in the thyroid gland is expelled by perchlorate or thiocyanate. Thus, if a dose of such a compound is given to an affected individual one hour after administration of radioactive iodide, there is a marked fall in counting rate over the thyroid. In normal individuals, all the radioactive iodide trapped by the gland is converted instantaneously into organic form and no such fall occurs.

The audiogram of cases of the Pendred syndrome characteristically shows complete sensorineural loss of hearing in the high frequencies, often with an island of residual hearing being retained in the low frequencies. This pattern is found in many types of autosomal recessive deafness, but the correspondence between the aetiology of hearing loss and audiometric patterns is in general not close and exceptions to this rule occur frequently in cases of the Pendred syndrome, as in other types of autosomal recessive deafness. There is no firm evidence as to whether progression of the hearing loss occurs in the Pendred syndrome.

**The Usher syndrome (deafness with retinitis pigmentosa)**

The Usher syndrome is one of the more common types of deafness in European populations, although it is less common than the Pendred syndrome. In 1858, only a few years after the discovery of the ophthalmoscope had made the detection of this syndrome possible, the famous German ophthalmologist, Albrecht von Graefe, briefly mentioned in a paper on retinitis pigmentosa that a cousin of his, Alfred Graefe, while assisting him in his Berlin clinic, had seen a sibship of five children in which three deaf brothers had the condition.

Liebreich (1861) systematically surveyed the deaf population of Berlin for retinitis pigmentosa and found that the association was more common among the Jewish deaf. Other early surveys of deaf populations were conducted by Adler (1876), Lee (1883) and Hammerschlag (1907). The last of these authors conducted a survey of deaf individuals in Vienna and confirmed the findings of Liebreich (1861), that the association with retinitis pigmentosa was more common among deaf persons who were Jewish.

In general, the different types of autosomal recessive deafness may vary greatly in frequency between population groups. These variations are associated with the fact that marriages do not occur at random within the human population and the choice of marriage partner may be constrained by religious, ethnic, social, or geographical factors. Because of these deviations from random mating (panmixia), abnormal alleles and the autosomal...
recessive conditions to which they give rise may reach high frequencies in certain groups. These are known as mating isolates because marriages often occur within the group (inbreeding). The Jews of Central Europe may have constituted one such isolate in which the allele for the Usher syndrome reached a high frequency. Another such isolate has been described more recently. In the Acadian population of Louisiana consisting of 57000 individuals, 44 cases of the Usher syndrome were identified (Kloepfer, Laguaite and McLaurin, 1966). This figure for the prevalence of the condition is far higher than any reported from other populations, and it must be assumed that one or more of the restricted number of founders of this isolated and inbred population carried the abnormal allele on arrival from the original home of the Acadians on the Eastern seabord of Canada. Subsequently, as population numbers grew in their new home, the condition reached its present high prevalence. This is known as a founder effect.

It was actually more than half a century later after the findings of von Graefe (1858) and Liebreich (1861) in Berlin that Usher (1914), in studying the incidence of deafness in a series of cases of retinitis pigmentosa referred to his ophthalmologic clinic in London, noted the existence of the syndrome which now carries his name. This eponym is probably best reserved for the autosomal recessive association of retinitis pigmentosa with profound childhood deafness, although the existence of genetical subtypes comprising milder deafness of later onset, and even a distinct mode of inheritance, has been postulated on inadequate grounds.

Typically, the sensorineural hearing loss in the Usher syndrome shows the same audiometric configuration as that in the Pendred syndrome, the high tones being more severely involved than the low, although many exceptions occur to this rule. Marked disturbances of vestibular function are commonly found.

Subjective and objective signs of retinal involvement usually do not appear until late childhood, or even adult life, unlike the deafness which is of very early onset and is usually diagnosed before the age of 3 years. Contraction of the visual fields (tunnel vision) and night blindness may precede objective evidence of retinitis pigmentosa as determined by ophthalmoscopy; when they occur, the ophthalmoscopic lesions are characteristically peripheral in distribution. It is probable that more sensitive electrodiagnostic tests, such as the electroretinogram (ERG) and the electrooculogram (EOG), would reveal abnormalities at a much earlier age, perhaps even at birth.

Cataracts are a common complication in later life and, in combination with progressive retinal degeneration, may lead to virtual blindness. Nevertheless, the prognosis for vision is not always poor since cataracts may never form and the retinal degeneration may remain stationary indefinitely. Thus, in some cases, Usher's syndrome may first be diagnosed in middle age, or even later, by routine ophthalmoscopy without the patient being aware of undue visual difficulties.

The Jervell and Lange-Nielsen syndrome
(deafness with electrocardiographic abnormalities)

Bizarre abnormalities of the electrocardiogram are associated with deafness in this condition which is less common than the syndromes of Usher and Pendred. The QT interval
is markedly prolonged due to lengthening of the ST segment and the T wave, with normal appearance and duration of the QRS complex. The large T waves may be upright, biphasic, or inverted. A disorder of the later stages of cardiac repolarization is probably the underlying cause of these very unusual anomalies. It gives rise to a susceptibility to episodes of ventricular fibrillation which are manifested as recurrent fainting attacks (being, in fact, attacks of cardiac syncope) beginning in early infancy. Any one of these attacks is potentially fatal and sudden death is a component of this autosomal recessive syndrome.

In view of the dramatic nature of this condition, it is perhaps surprising that its recognition and delineation had to await the published description of Jervell and Lange-Nielsen (1957). These authors described a family in Norway in which four of six sibs were deaf. From early childhood all four had been subject to fainting attacks during which three had died at the ages of 4, 5 and 9 years. Of course, the recognition of the syndrome was not possible before the discovery of the electrocardiograph and, in addition, sudden death in childhood has been more common than it is now and, therefore, attracted less interest. In addition, the taking of an electrocardiogram may not form part of the routine investigation of recurrent fainting attacks which tend to be ascribed to neurological or even psychological causes. It was only because Jervell and Lange-Nielsen showed unusual perspicacity in obtaining ECGs from their patients that they were able to characterize the syndrome which now bears their name. There are, in fact, several suggestive accounts in the earlier literature of sudden death in deaf children which may well represent this condition, the first being reported by Meissner in 1856, long before the discovery of the electrocardiograph.

In the past, a substantial proportion of individuals with this syndrome died before reaching adolescence. A process of gradual adaptation to the disorder of cardiac conduction occurs so that, once adolescence is reached, the frequency of the fainting attacks is much diminished and the danger of sudden death recedes. The prognosis in childhood has improved greatly with modern treatment with drugs, and with the use of the implantable automatic defibrillator.

The hearing loss is characteristically similar to that seen in the syndromes of Pendred and Usher with complete loss of hearing in the high tones and some retention in the low.

**Other autosomal recessive syndromes including deafness**

There are only three autosomal recessive syndromes currently identified (those of Pendred, of Usher, and of Jervell and Lange-Nielsen) which are at all common among deaf persons. Other autosomal recessive syndromes involving deafness are much less frequent, and even their status as distinct entities is in doubt in many cases. The reason for these uncertainties is simple. Autosomal recessive deafness, as a whole, is a relatively common condition and it is not surprising, therefore, that, among the many thousands of persons with this handicap who have been studied, some should fortuitously be affected with other genetically-determined traits.

It is pertinent to consider at this stage the criteria on which the definition of the associations of deafness with goitre, with retinitis pigmentosa, and with ECG abnormalities as autosomal recessive syndromes is based. In each case, many families have been described in which multiple sibs suffer from the association in question. In these families, persons do
not have deafness without the associated abnormality and vice versa. Even though no concrete knowledge exists concerning the biochemical mechanisms through which the abnormal alleles in question exert their pleiotropic effects (that is effects on different organ systems), it would be stretching coincidence too far to suppose that deafness and the associated abnormality were present in the same persons fortuitously in all cases. An alternative hypothesis to that of pleiotropism of abnormal alleles in the homozygous state at a single locus is that closely linked loci are responsible for the deafness and the associated abnormality. Experimental breeding techniques are not, of course, available in man and, therefore, such a theory cannot be formally invalidated but, in the light of current knowledge concerning gene action, the hypothesis of pleiotropism provides a far more likely explanation.

The number of such syndromes involving deafness which have been tentatively defined is very large and little would be gained by deriving a listing from various compilations which are available (Fraser, 1976; Konigsmark and Gorlin, 1976; McKusick, 1986). It should be noted that in many of these syndromes the hearing loss is rarely or never profound in childhood. Instead of such a listing, one syndrome will be mentioned since it illustrates some basic principles concerning the genetics of deafness. This is the multiple malformation syndrome, sometimes known as the cryptophthalmos syndrome after one of its most striking component features.

The cryptophthalmos syndrome; modes of gene action and deafness

Cryptophthalmos means hidden eye and, in a fully expressed case, the eyelids are fused and the ocular globe is represented only by some disorganized remnants. This cardinal feature illustrates the principle of variability of expressivity of the abnormal allele in this condition. The extent of the eye involvement is variable and sometimes the eyelids and ocular globe may be virtually normal, giving rise to the paradox that the cryptophthalmos syndrome may exist without the presence of cryptophthalmos. In such a case, the diagnosis must be made by identifying some of the large number of other malformations, affecting virtually all organ systems, which may occur in this condition. Not only its presence, but also the degree to which each of these malformations is expressed is variable, giving rise to an almost infinite range of clinical manifestations, or phenotypes. The involvement of the auditory apparatus in this condition is as variable as that of any other organ system. Deafness, when it occurs, may be profound and is associated with malformations of the middle ear ossicles. Thus, it is conductive rather than sensorineural; this is true of only a small minority of cases of genetically-determined profound deafness in childhood.

It is perhaps surprising that only one of all these malformations is potentially lethal - renal dysplasia. Thus, stillbirths or neonatal deaths are seen in a substantial proportion of cases of the cryptophthalmos syndrome and are associated with renal aplasia, an extreme degree of this malformation. The cryptophthalmos syndrome may therefore be regarded as a semi-lethal genetic condition, one of a number of autosomal recessive multiple malformation syndromes with a limited potential for survival. Of course, semi-lethal abnormal alleles do not necessarily cause multiple malformations. The syndrome of Jervell and Lange-Nielsen, described above, may also be regarded as being the result of such an allele.

It is reasonable to assume that biochemical defects are involved in the causation of the syndrome of Jervell and Lange-Nielsen and of the syndromes of Pendred and of Usher, even
though nothing is known of the nature of such defects, which may be presumed to be caused by the absence of normal alleles at the gene loci in question. However, by analogy with other autosomal recessive conditions such as galactosaemia, phenylketonuria and sickle-cell anaemia, which also comprise constellations of widely disparate clinical manifestations, it seems likely that point mutations in the chromosomal DNA have led to amino acid substitutions in an essential protein whose deranged function gives rise to deafness and its accompanying manifestations in these three syndromes.

It should be noted that, at a time when the nature of these biochemical defects will be elucidated, which may be far in the future, much will be learnt about the mechanisms of normal and abnormal hearing, cardiac conduction, thyroid hormone synthesis, and retinal function. Such discoveries will also have profound implications with respect to the treatment of deafness. In this context, it has been noted above that it is not known whether these abnormal alleles exert their full effect on the auditory apparatus in fetal life, or soon after birth. In the mouse, where detailed histological studies of the auditory apparatus are possible, both types of abnormal alleles are known. If the main brunt of the damage is in fact postnatal, this would be encouraging for prospects of prevention of deafness on the model of the dietary treatment of phenyloketonuria; in this autosomal recessive condition damage to the brain occurs after birth unless a phenylalanine-free diet is provided.

In the case of the cryptophthalmos syndrome such a ‘simple’ biochemical explanation seems unlikely. Perhaps a whole region of the chromosome rather than a single DNA base pair is involved. Such a chromosomal lesion must be presumed to be beyond the present resolving power of cytogenetical techniques but this need not always be the case. Lesions of this type in a particular chromosomal region may well be variable in extent, giving rise to the wide clinical diversity which has been observed in the cryptophthalmos syndrome and which occurs mainly between, rather than within, families, as is to be expected on the basis of such a hypothesis. Thus, although variable between families, the particular genetical constitution, or genotype, within a family will be associated with a particular pair of small abnormal allelic chromosomal regions which will be constantly present in affected members of the same family.

**Clinically undifferentiated (non-syndromal) autosomal recessive deafness**

Despite the large number of syndromes mentioned above, the great majority of cases of deafness caused by autosomal recessive inheritance are clinically undifferentiated - the deafness does not form part of a recognizable syndrome in which it is associated with visible malformation or in which other organs and body systems are involved. There are undoubtedly several gene loci at which autosomal recessive non-syndromal deafness may be determined. Thus, it has been mentioned above that marriages between individuals both of whom have an unequivocal family history indicative of such a condition (consanguineous parents or affected siblings) most often give rise to offspring who are hearing. This suggests that these offspring are doubly heterozygous at the two gene loci at which the deafness of their parents is caused. Only in rare families are all the offspring deaf suggesting that the same locus is involved.

Another line of evidence suggesting that there are multiple gene loci involved is the consanguinity rate among the parents of children with non-syndromal autosomal recessive deafness. The rarer an autosomal recessive condition, the higher is the rate of consanguinity
among the parents because the chance of an unrelated marriage partner carrying the same abnormal allele decreases with its frequency. The consanguinity rate among the parents of children with autosomal recessive non-syndromal deafness is higher than would be expected if this were a single condition, suggesting that it is made up of a number of component entities.

It is very difficult from these types of evidence to make an estimate of the number of gene loci which may be involved in the causation of non-syndromal autosomal recessive deafness. Fraser (1976) has suggested that there may be two or three relatively common types with a prevalence in the population of the UK similar to that of the Pendred syndrome, two or three moderately common types with a prevalence similar to that of the Usher syndrome, and up to 12 rarer types of which the syndrome of Jervell and Lange-Nielsen is an example.

**Autosomal dominant deafness**

Mendelian dominant inheritance of deafness occurs when a single abnormal allele is sufficient to cause the condition, even in the presence of a normal allele of the same locus on the paired chromosome. Thus, affected individuals are heterozygous at the locus in question and they pass the abnormal allele on to one-half of their offspring. Not all of these offspring are profoundly and bilaterally deaf, however, since the abnormal allele does not give rise to its full potential adverse effect in every individual who carries it. Thus, the deafness may vary from profound to mild, and may be unilateral rather than bilateral. This is known as variable expressivity of the abnormal allele. Some individuals may escape the effects of the abnormal allele altogether and enjoy normal hearing. This is known as reduced penetrance.

Autosomal dominant deafness, like the recessive variety, is extremely heterogenous and distinct abnormal alleles at many different loci may be involved. The degrees of expressivity and penetrance of these abnormal alleles vary widely and, as a result, some families will show the classical pattern of Mendelian autosomal dominant inheritance with full expressivity and penetrance through several generations. In such families, on average, one-half of the offspring of affected individuals manifest profound bilateral deafness.

**The Waardenburg syndrome**

Of all the syndromes of which deafness is a component, this is the best known because of the striking anomalies of pigmentation which occur in association with hearing impairment. Heterochromia of the irides may be present and is often very striking, one eye showing a deep blue pigmentation and the other a deep brown. It may be partial rather than total with segments of two different colours in one or both eyes. In addition, there may be partial hypopigmentation of skin, eyebrows, ocular fundi, and hair (white forelock). Even if the irides are not heterochromic, they may often show an unusual blue colour, associated with hypopigmentation and hypoplasia of the stroma. Other features include overgrowth of the eyebrows leading to confluence, a broad and prominent root of the nose and a peculiar configuration of the eyelids associated with lateral displacement of the medial canthi (telecanthus or dystopia canthi medialis lateroversa).

There are many indications in the earlier literature of the existence of such a syndrome, but it was Waardenburg, in 1951, who first clearly delineated all the clinical
features of this autosomal dominant condition which now bears his name as an eponym. Many families have since been reported coming from all ethnic groups (the condition is one of the causes of the rare appearance of blue eyes in non-white individuals). It has become clear, as Waardenburg (1951) had suggested, that there is genetic heterogeneity even within this very specific association of hearing impairment with pigmentary anomalies, in that at least two distinct clinical forms, or phenotypes, are to be found. The main distinguishing feature between these two forms is the presence or absence of lateral displacement of the medial canthi. Within a single family, only one form occurs in affected individuals, suggesting that different alleles, and possibly even different gene loci, are involved.

Variable expressivity and reduced penetrance of these abnormal alleles are commonly found in the Waardenburg syndrome and may affect each clinical manifestation independently. Thus, some individuals may escape the effect on hearing of the abnormal allele altogether (reduced penetrance) or may be unilaterally or mildly deaf, but still show clearly that they are transmitting the allele responsible because of the presence of pigmentary anomalies. When the deafness is bilateral and profound, it is often similar to that seen in autosomal recessive deafness with only a residual island of hearing being preserved in the low tones. When the hearing loss is more moderate, the audiogram often shows a flatter pattern; there is even sometimes an improvement in the high tones.

The Treacher Collins syndrome

The Treacher Collins syndrome (mandibulofacial dysostosis)(Collins, 1900) is a well-known but rare cause of profound deafness. The complete syndrome consists of abnormalities of the outer, the middle, and occasionally the inner ears, associated with antimongoloid palpebral fissures, colobomas of the lower eyelids, hypoplasia of the malar bone and mandible, macrostomia, high palate and malformed teeth, blind fistulae between the angles of the mouth and the ears, and abnormal implantation of the facial hair. These deformities may occur in any combination and with varying degrees of severity; they may be unilateral. The deafness is usually conductive since involvement of the inner ear is unusual, and it is only rarely bilateral and profound. The condition is autosomal dominant, but is often difficult to trace through several generations because of variable expressivity and reduced penetrance of the abnormal allele concerned. Furthermore, a substantial proportion of cases described seem to be due to fresh mutations; that is to say that the abnormal allele first appeared in the germ cell derived from one or other of the parents who are not themselves affected since they do not carry the abnormal allele in their somatic cells.

Other autosomal dominant syndromes including deafness

As in the case of autosomal recessive deafness, there are many of these syndromes and descriptions may be found in the compilations mentioned above. The Alport syndrome of sensorineural deafness with nephritis is very well known but virtually never leads to profound hearing impairment in childhood, the deafness typically being initially mild with an onset in late childhood or adolescence and with subsequent progression.
Clinically undifferentiated (non-syndromal) autosomal dominant deafness

As in the case of autosomal recessive non-syndromal deafness, there is likely to be genetical heterogeneity in the autosomal dominant variety. This is strongly suggested by the variability of audiometric pattern and degree of hearing loss, the variation being more marked between than within families, suggesting that different alleles may be at the origin of such variation. This is also true of the familial patterns of variable expressivity, reflected in unilateral involvement, and failure of penetrance, reflected in the presence of family members who have normal hearing but who have transmitted the abnormal allele.

As in autosomal recessive non-syndromal deafness, cases of the autosomal dominant variety are often isolated in one family. This may be because they represent fresh mutations, or it may occur because the allele has not been recognized to be present in other family members because of variable expressivity or reduced penetrance.

X-linked deafness

In 1836, at the very beginning of serious scientific inquiry concerning the subject of the causation of deafness, Kramer wrote as follows in discussing hereditary predisposition:

'Most frequently the parents of deaf-dumb children hear perfectly well; in this respect nature often observes the most strange and inexplicable laws of formation, for the determination of which we have no data. In place of many similar instances, I may merely detail one which comes under my notice every day. A man and his wife, of the name of Hartnuss, of Berlin, both of them healthy and having no predisposition to any disease of the ear in their family on either side, have five daughters and six sons; the latter were all born deaf-dumb, whilst the daughters, without exception, hear perfectly well. The mother of these eleven children is not aware of any circumstances that distinguish her pregnancies from each other, though the children are so remarkably differently endowed.'

It seems very likely that this family represents X-linked deafness, but because such patterns characteristic of X-linked inheritance (occurrence in males with transmission by unaffected females) have only rarely been reported, deafness of this type is probably very uncommon. References are to be found in Fraser (1976) where some additional pedigrees are presented. It is there pointed out that sibships containing two or more deaf brothers without deaf sisters were observed in a survey of the population of the British Isles with greater frequency than is to be expected, suggesting that some owe their deafness to X-linked rather than autosomal recessive inheritance.

X-linked syndromes including deafness

A strikingly rare pedigree described in Israel by Ziprkowski et al (1962) and by Margolis (1962) showed an association of deafness with pigmentary anomalies reminiscent of the Waardenburg syndrome. In this family, however, the association was clearly inherited in an X-linked recessive, as opposed to an autosomal dominant manner.

While most X-linked deafness is sensorineural, Nance et al (1971), in a careful study of a family in which profound deafness was segregating in a pattern consistent with X-linked
inheritance, showed that the hearing loss in six affected males was of a mixed type with both conductive and perceptive components. Furthermore, at operation in one case, a fixation of the footplate of the stapes was found. In addition, operation was complicated by a profuse flow of perilymphatic fluid thought to be under increased pressure as a result of an abnormal patency of the cochlear aqueduct.

**A spectrum of Mendelian causation**

It has been shown that deafness inherited in a Mendelian manner is very heterogeneous. It is extremely difficult to establish a balance sheet of causes, especially since these may vary substantially between populations. Furthermore, the methods available for establishing such a balance sheet are very limited since virtually nothing is known of the mode of action of the genes involved and only very partial clinical differentiation is possible.

Fraser (1976) in a study of the causation of deafness in the British Isles concluded that about one-half of all cases were determined in a Mendelian manner. This would give a population prevalence for Mendelian deafness in childhood of about 1 in 2000. Of these cases, about 66% were determined in an autosomal recessive manner, 31% in an autosomal dominant, and 3% in an X-linked recessive manner. Of the autosomal recessive cases, the syndromes of Pendred, Usher and Jervell and Lange-Nielsen accounted for 17, 9 and 2% respectively while, of the autosomal dominant cases, syndromes involving associated disorders of pigmentation such as that of Waardenburg accounted for 20%. These can only be regarded as very rough guidelines but, taking into account the large number of rarer syndromes, and the fact that the majority of cases of Mendelian deafness are non-syndromal and may be determined at many different loci, these figures are indicative of the considerable genetical heterogeneity underlying what is biologically a homogeneous handicap.

**Congenital malformations and deafness**

The Treacher Collins syndrome has been mentioned as an autosomal dominant congenital malformation syndrome which may include deafness as one of its components and the cryptophthalmos syndrome as an autosomal recessive one. Many other such syndromes, both dominant and recessive, have been described. A substantial proportion of cases in which deafness occurs as part of a congenital malformation syndrome are not determined in a simple Mendelian manner, but must be assumed to be caused by the synergistic interaction of multiple genes modified by environmental factors. An example of this group of conditions may well be the Wildervanck (1960) syndrome which combines hearing loss, associated with malformations of the outer, middle and/or internal ear, with Klippel-Feil anomaly of the spine. Although the malformation itself seems to occur with equal frequency in the two sexes, its association with impaired hearing occurs much more often in girls, in a ratio of 10 or more to one boy. The reason for this is not clear but a predilection for one or other sex is a characteristic feature of congenital malformations as a whole, although it is usually less pronounced.

Presumably, this phenomenon is due to the fact that one sex has a lower threshold of resistance to the combination of genetic and environmental factors determining a particular defect of embryogenesis. Since embryogenesis takes a substantially different course in the two
sexes, such variations in resistance would not be surprising. The Wildervanck syndrome in fact accounts for 2% of deafness among girls.

The genetic component contributing to acquired forms of deafness

As much as one-half of cases of profound deafness in childhood are due primarily to acquired causes but the contributory hereditary component should not be forgotten. Thus, susceptibility to the teratogenic effects of the rubella virus is to some extent dependent on the genotypes of both mother and fetus. Deafness connected with perinatal mishaps is also due in part to genetic factors which may include those associated with low birthweight and those which determine the nature and extent of susceptibility to ototoxic drugs. Meningitis is a common cause of deafness acquired in early childhood. Again, genetic factors intervene in determining susceptibility both to the infecting organism and to ototoxic drugs used in treatment. Such genetic determinants in primarily acquired deafness are not easy to define but they are, nonetheless, of considerable importance.