Review Article

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Profound Childhood Deafness*

G. R. FRASER

From the Godfrey Robinson Memorial Unit, Department of Ophthalmology, Royal College of Surgeons, London W.C.2

> 'It will be a great step forward when the physician takes part in the work for defectives who have hitherto been entrusted wholly to teachers in schools.... The problems of deafness are deeper and more complex, if not more important, than those of blindness. Deafness is a much worse misfortune. For it means loss of the most vital stimulus—the sound of the voice—that brings language, sets thought astir and keeps us in the intellectual company of man.'
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> From *The Deaf Child*, by J. Kerr Love, Simpkin and Co., London, 1911.

Definition and Introduction

The term profound childhood deafness is used in preference to the old-established one of deaf-mutism, since it is now clear that, contrary to the accepted dogma current from antiquity to recent times, mutism is not due to a pathological lesion of the speech apparatus associated with failure to hear, but to a lack of suitable training which can often be remedied. Profound childhood deafness is a socio-educational entity and may be defined as deafness with an early enough onset and of sufficient degree to necessitate the use of special or supplementary methods for the learning of speech. This definition excludes the very common deafness of adult life often inherited in a dominant manner, whether conductive (otosclerosis) or perceptive. Many rare genetical syndromes are also excluded of which deafness of a less severe nature and/or of late onset is a component part. These include such recessive syndromes as perceptive deafness, atypical retinitis pigmentosa, chronic polyneuritis and ataxia (Refsum, Salomonsen, and Skatvedt, 1949), and perceptive deafness with optic atrophy and diabetes (Shaw and Duncan, 1958), with diabetes mellitus, retinal degeneration, and obesity (Alström, Hallgren, Nilsson, and Åsander, 1959) with congenital facial paralysis (Thomas, 1898; Cadwalader, 1922), and many others; in addition, the dominant syndromes of perceptive deafness with nephritis (Alport, 1927), with auditory neurofibromata (Gardner and Frazier, 1930), and with ectodermal dysplasia (Helweg-Larsen and Ludvigsen, 1946; Robinson, Miller, and Bensimon, 1962) and others, and of conductive deafness with osteogenesis imperfecta (van der Hoeve and de Kleijn, 1917). Occasionally profound childhood deafness will occur in association with one of these conditions; conversely, persons will occasionally suffer from only mild losses of hearing in association with syndromes more usually associated with profound childhood deafness. No biological classification can be expected to follow very closely lines of demarcation defined on the basis of socio-educational criteria. There is even no absolute correlation between educational segregation and degree of hearing loss. Thus severe hearing loss in infancy is sometimes compatible with normal education, and special schooling may occasionally be necessary with a relatively mild deafness. Other, as yet ill-understood, factors may condition the extent of the child's adaptation to the hearing loss.

Many other difficulties stand in the way of an unambiguous biological classification of profound childhood deafness. Thus an unequivocal differentiation between congenital and postnatal onset is often impossible, since the diagnosis of deafness may only be made when speech fails to develop normally in the first two years of life or even later. Furthermore, congenital and postnatal deafness cannot be equated simply with genetical and acquired forms. Congenital deafness may be due to maternal rubella, and, owing to diagnostic difficulties in infancy, evidence is lacking as to whether genetical childhood deafness is in fact usually congenital or rapidly progressive in early life.

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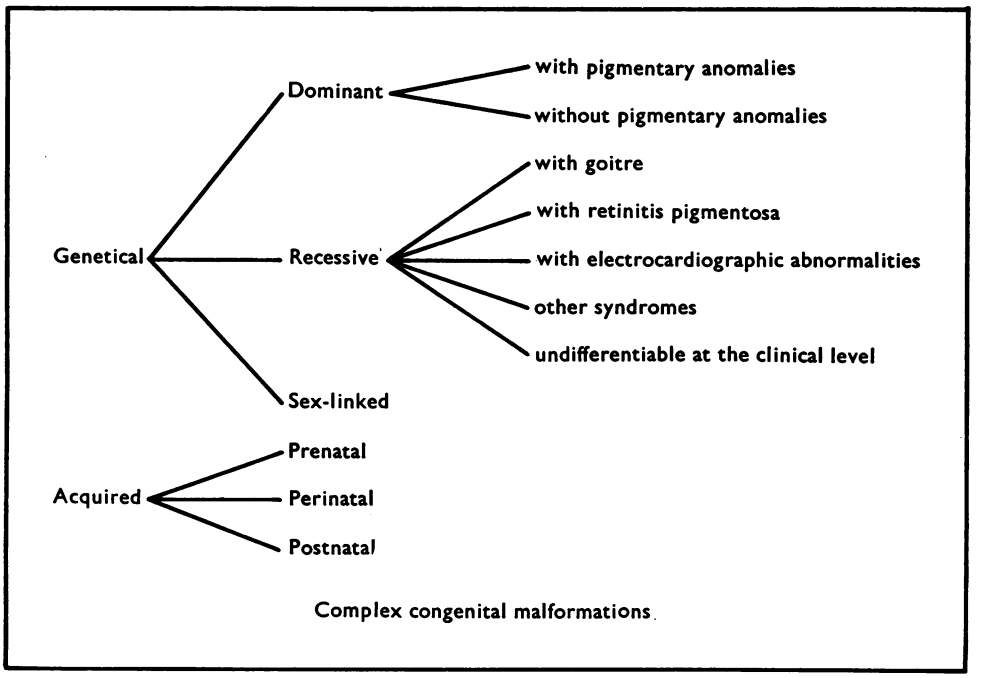

The latter situation is certainly common in the case of recessive deafness in mice (Deol, 1954). In these animals rapid degeneration of morphologically normal labyrinthine structures takes place when the appropriate genotype is present. In man it is known that dominant perceptive deafness is often progressive (Stephens and Dolowitz, 1949) and, in fact, this is characteristically a disease of adult life. Rarer examples of apparently progressive recessive deafness are also known, either isolated (de Kleyn, 1915) or in association with other abnormalities such as the Laurence-Moon-Biedl syndrome (Burn, 1950; Graf, 1964).

These difficulties were clearly perceived as long ago as 1821 by Itard, who, writing of the distinction between congenital and acquired forms, said that the causes of profound childhood deafness would never be more than imperfectly known. This judgement, while remaining often valid in the individual case, is to a great extent no longer so if applied to profoundly deaf children as a whole. By means of thorough clinical, genetical, and statistical studies of such populations, a reasonably accurate picture of the spectrum of causes can be obtained and informed estimates be made of their relative importance.

While the main emphasis of this review bears on genetical causes of profound childhood deafness, exogenous causes, whether acting in the pre-, peri-, or postnatal period cannot be ignored, both because of diagnostic difficulties in the individual case and because of their intrinsic interest as a whole. As Hopkins (1954) wrote; 'Any study of the inheritance of deafness must in reality be a study of the different types of deafness.' The schema above represents an attempt at biological classification on which the present review is based. The dichotomy, much used in the past, between congenital and acquired deafness is discarded altogether. It should be noted that whenever deafness is mentioned in this review, unless explicitly otherwise qualified, the entity of profound perceptive childhood deafness is meant.

Historical Note

Since it was thought on the august authority of Hippocrates and Aristotle that those born deaf were unable to speak because of an irreparable organic lesion, no attempt was made to teach speech to profoundly deaf children until the 16th century. At this time Pedro de Ponce, surnamed Venerabilis, a Benedictine monk, achieved great renown by teaching the profoundly deaf scions of several noble Spanish families to speak. An excellent discussion of the problems of profound childhood

deafness up to and including this period is to be found in the book of Werner (1932).

Following Pedro de Ponce, rapid advances were made in the provision of educational facilities for profoundly deaf children and, *pari passu*, interest was aroused in wider problems of the causation and dissemination of this condition. In the 19th century profound childhood deafness was in the forefront of scientific medical inquiry. Through the exertions of governments, the Church, private individuals, and charitable institutions, very complete censuses of the deaf were made in most of the states of Europe, and in the U.S.A., and thorough analyses were made of the causes of deafness acquired in childhood.

Furthermore, both medical men and educators became very interested in the aetiology of other types of deafness and, though, in the pre-Mendelian era, the mechanism of recessive inheritance was unknown to them, they appreciated the possible importance of such factors as parental age, birth rank, and prematurity. In 1846, moreover, both Puybonnieux and Menière in France stressed the importance of consanguineous unions in predisposing to deafness among the offspring.

This condition in fact provided for many years the main battleground for a great philosophical polemic between 'consanguinists' and 'anti-consanguinists'. Anti-consanguinists were able for some time to uncover biased statistics in support of their point of view that consanguineous marriages were not of importance in the causation of deafness and other ills, and that the percentage of such unions among the parents of the congenitally deaf was not unduly high. Their discomfiture, however, was only a matter of time, and in 1879 Mygge, by a careful and methodical analysis of all available data, was able to demonstrate conclusively that these ideas were false and that, in fact, matings between relatives were more likely to produce deaf children than those between unrelated persons. This controversy is extensively discussed in the thesis of Sambuc (1896).

Many other excellent works on statistical and aetiological aspects of profound childhood deafness appeared in the 19th century, sometimes as philosophical dissertations, sometimes as reports of censuses of particular deaf populations and sometimes as sections of textbooks devoted to the study of ear diseases. Only a few of the more notable ones can be mentioned here, such as those of Itard (1821), Menière (1846, 1856), Puybonnieux (1846), and Saint Hilaire (1900) in France; Sauveur (1847) in Belgium; Schmalz (1830, 1838), Kramer (1835), Meissner (1856), Wilhelmi (1873), Hartmann and Wilhelmi (1880), Hartmann (1881), Hedinger (1882), Schmaltz (1884), and Lemcke (1892) in the provinces of Germany; Bell (1883) and Fay (1898) in the U.S.A.; Wilde (1853) and Purdon (1867) in Ireland; and Scott (1844), Toynbee (1860), and Love (1896) in England and Scotland. The interest which the subject aroused may be gauged by the fact that Meissner was already able in 1856 to provide 53 pages of bibliography. This entire literature was most ably reviewed in two remarkable books by Mygind (1894) and Uchermann (1901), who were themselves responsible for surveys of deaf populations in Denmark and Norway respectively. At the beginning of our century the time was ripe to apply the ferment of the newly discovered laws of Mendel to the very solid foundations constructed by these able and painstaking investigators.

I: Genetically Determined Deafness

Mode of Inheritance. It had, of course, been noted in the 19th century and even earlier that profound childhood deafness tended to affect more than one child in a sibship. Since, however, only direct transmission from parent to child was regarded as strictly hereditary, recessive deafness was ascribed to the influence of an inherited but arcane predisposition transmitted through the parents and often manifested by insanity, epilepsy, and a host of other abnormalities (Mygind, 1894). The merit of Mendel's laws as applied to this problem was that they could explain the nature of this mysterious predisposition as heterozygosis for an abnormal gene, clinically without effect in the parents, which in homozygous form produced deafness in a proportion of the offspring. Furthermore, in this way, the phenomenon that consanguineous marriages were represented to an unduly high extent among the parents of the deaf also fell naturally into place, since the relatives of a carrier of a rare gene would have a high chance of being carriers themselves.

Lundborg (1912, 1920) was one of the earliest investigators to apply himself to the problem of studying the exact modality of the inheritance of deafness using, among others, the data of Fay (1898). He and many after him, such as Kraatz (1925), made the very natural mistake that they transposed the clinical homogeneity of profound childhood deafness to the biological level. Lundborg, therefore, came to the conclusion that all cases of congenital deafness were recessive and due to only one abnormal gene. It soon became clear that this was an oversimplification. Jenkins as

early as 1891, writing of heredity in its relation to deafness, had said that 'deafness no more implies one defect or disease than cough or jaundice does.... Congenital deafness is due not to one but to many different and unconnected pathological conditions.'

Dahlberg (1931) attempted a comprehensive treatment of the problem from the point of view of the geneticist. He pointed out that to fit the oversimplified hypotheses of such authors as Lundborg, Hammerschlag, Orth, Plate, Bauer, and Stein, which are fully discussed and described, the available data had to be distorted beyond recognition. He proposed a more complex system and, while he did clearly envisage the heterogeneity of the problem, his theory of the aetiology of inherited deafness as a 'polyhybrid' interaction between several genes, some in heterozygous (dominant factors) and some in homozygous (recessive factors) form, has not withstood the test of time.

Several families were described in which the offspring of parents, both of whom unequivocally suffered from recessive deafness, were normal (Mühlmann, 1930; Csörsz and Tokay, 1934; Hammerschlag, 1934; Lehmann, 1950) and this raised the possibility that in fact a great number of different genes were involved, each of them capable of causing deafness in the homozygous state. The necessity of postulating complex interactions and polyhybrid inheritance was thus eliminated.

This interpretation is supported by the results of many complete family surveys of deaf populations, some restricted to small inbred isolates (Albrecht, 1922, in Germany; Hanhart, 1938; Secrétan, 1954; Pfändler, 1960; Pfändler and Stucki, 1960; and Pfändler and Schnyder, 1960, in Switzerland), and others to entire provinces or even countries (Lindenov, 1945, in Denmark; Stevenson and Cheeseman, 1956, in Northern Ireland; Furusho, 1957, in Kyushu, Japan; Aulbers, 1959, in South Holland; Deraemaeker, 1960, in North Belgium; and Sank, 1963, in New York, U.S.A.). Though these authors come to somewhat conflicting conclusions, it is clear that in fact several different genetical types of recessive deafness exist and that no interaction takes place between the genes causing them. The number of genes involved naturally varies with the geographical extent of the population studied and with demographic factors, such as the degree of inbreeding. Thus while the data of Furusho (1957) are consistent with the involvement of only one gene, many must be implicated in the data of Stevenson and Cheeseman (1956). These latter data have been the subject of several mathematical analyses. Slatis (1958) adhered to the now generally discredited idea of polygenic inheritance, i.e. interactions between genes at different loci, but Chung, Robison, and Morton (1959) in a classical analysis showed that the data were consistent with the existence of very many (up to 36) different autosomal loci at each of which abnormal genes could determine recessive deafness independently, and that dominant and sex-linked forms were also involved. Sank (1963) concluded that an even greater number (at least 45) of different genes were implicated in the causation of recessive deafness and also stressed the importance of dominant forms.

This situation is very similar to that in mice where, unlike man, it can be clarified by experimental breeding and by tests of allelism and linkage. A large number of genes causing recessive deafness have been described (Grüneberg, 1956; Deol, 1954, 1956a, 1956b, 1963; Deol and Kocher, 1958; Deol and Robins, 1962; Kocher, 1960a, 1960b). Interactions between these genes are uncommon, but occasionally double heterozygotes will become deaf in later life (Lord and Gates, 1929; Deol, 1956a); early deafness, the analogue of profound childhood deafness in man, does not occur, however, in such double heterozygotes.

At the present time the main interest in the subject of profound childhood deafness in man lies in the identification and characterization of the various genes concerned in its causation. Man has some advantages, as well as disadvantages, over mice as an organism for genetical studies. First, much more is known of normal human physiology and biochemistry and of pathological aberrations, and, secondly, accurate pedigree data have been kept in some areas, at least, for many generations. Furthermore, though experimental breeding is out of the question as a tool for analysis, the deaf in fact marry almost exclusively among themselves by choice. As their social integration proceeds, especially in economically advanced areas of the world, their fertility is approaching normal levels (Rainer and Deming, 1963), and these highly assortative mating patterns are producing an increasing number of informative families whose analysis can help in the identification of the various components of the heterogeneous entity of profound childhood deafness.

While in the methodologically related field of mental deficiency the main emphasis has been on biochemical differentiation between the various genes involved (phenylketonuria, galactosaemia, etc.), among the deaf such differentiation has so

far been successful only at the clinical level. It is remarkable how successful this has in fact been, considering that the organ directly affected, the inner ear, is not accessible to direct inspection as is, for example, the eye in the context of another methodologically related field, the analysis of the various clinical entities causing childhood blindness.

Despite these disadvantages, a large number of different genetical syndromes has been delineated which have only congenital deafness in common, accompanied by an extraordinary variety of other defects. While, thus far, cases of undifferentiated, clinically unidentifiable 'simple' genetical deafness remain in the majority, it is to be hoped that, as the biochemical basis of these syndromes becomes apparent, so the nature and heterogeneity of the genetical processes involved in the causation of deafness will be revealed. Elucidation of the basis of this pleiotropism of gene action cannot fail but throw much light on many obscure aspects of normal and abnormal human biochemistry and physiology. In the individual case such differentiation can be of vital importance from the point of view of prognosis for subsequent sibs and offspring and the vast problems of treatment, cure, and prevention can hardly be broached until these facts about causation are established.

Insufficient appreciation of the heterogeneity of profound childhood deafness may lead to difficulties in the analysis of population data. Thus the surveys of Pfändler (1960), Pfändler and Schnyder (1960), and Pfändler and Stucki (1960) in various areas of Eastern Switzerland reveal a great excess of sibship containing isolated cases of profound childhood deafness. As a result the ratios of affected to normal offspring in these sibships are lower than those expected on the hypothesis of recessive inheritance, and these authors are led to postulate various subsidiary hypotheses regarding the semi-lethality of the genes concerned, a situation that has not been described elsewhere, except in the context of a very well-defined clinical syndrome (see page 127) which these data do not suggest.

Such hypotheses are not only somewhat implausible but unnecessary since it is not improbable that some of the cases of profound childhood deafness are in fact due to exogenous causes acting very early in life and causing deafness superficially indistinguishable from the recessive variety. This is especially true of persons who had been ascertained only from Church books and had long been dead at the time of survey. This conclusion is strengthened by the excess of males among the deaf, for acquired deafness affects males preferentially (see page 132). Values approaching Mendelian ratios much more closely can be obtained from these data by the simple expedient of only assuming recessive inheritance in sibships containing at least two affected members. Great caution is mandatory in any such analysis of deaf populations, and clinical distinctions can often be of much help in defining the cause of deafness. Certainly it would be dangerous to argue from these data that a unique mutant allele with semi-lethal effects in foetal life is responsible for recessive deafness in Eastern Switzerland.

The preliminary results of a survey of a large population of deaf schoolchildren using clinical, genetical, and statistical methods of analysis have been published (Fraser, 1962a, 1964a). From these results it is clear that genetically determined causes are responsible for only about a half of all cases of profound childhood deafness and that as much as one-sixth of all cases may be due to pre- and perinatal exogenous causes which can easily cause confusion. Three relatively common genes which give rise to readily distinguishable clinical syndromes account for at least 25% of all cases of autosomal recessive deafness, this being the most common mode of inheritance involved in the causation of childhood profound deafness. Dominant and sex-linked recessive forms are also of importance.

The Syndrome of Retinitis Pigmentosa with Deafness. Of these three recessive syndromes, that of deafness with retinitis pigmentosa holds pride of place from the point of view of priority of discovery and thorough clinical description. It was only a few years after the discovery of the ophthalmoscope that von Graefe in 1858 in Berlin mentioned briefly a sibship in which 4 of 6 sibs suffered from this condition. A very much more thorough survey was made in 1861, also in Berlin, by Liebreich (Fig. 1). This author examined a deaf population systematically and was much struck by the high frequency of retinitis pigmentosa that he found, especially among the Jewish deaf. His data were also remarkable for the large number of consanguineous unions among the parents of affected persons.

Liebreich's (1861) survey served as a model for other studies regarding the frequency of retinitis pigmentosa in the deaf, among the earlier of which may be mentioned those of Adler (1876) and of Lee (1883). Hammerschlag (1907) confirmed, in Vienna, Liebreich's (1861) finding that this syndrome was more common among the

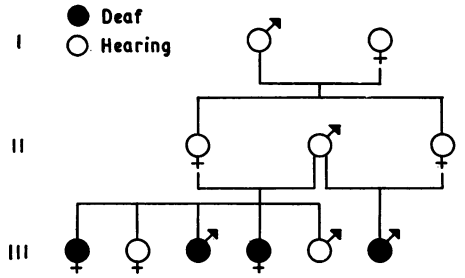

FIG. 1. Recessive inheritance of the syndrome of deafness with retinitis pigmentosa among the offspring of both unions between a man and two sisters after the data of Liebreich (1861).

Jewish deaf. More recently the survey of Lindenov (1945) among Danish deaf adults has revealed the considerable numerical importance of this syndrome as has the definitive monograph of Hallgren (1959), which described a complete country-wide ascertainment from Sweden.

The converse approach has also been attempted and various workers have estimated the frequency of deafness among those affected with retinitis pigmentosa. The methodology of such attempts is, of necessity, less satisfactory since persons with retinitis pigmentosa do not form a socio-educational isolate like the deaf and are therefore not readily accessible to complete ascertainment. The series that are available are usually of cases coming to the clinical attention of ophthalmologists, whether personal or collected from the published reports. Among the larger of these surveys are those of Nettleship (1907–08), Usher (1914) (who gave his name as an eponym to this syndrome, though the claim of Liebreich is considerably stronger), Bell (1922), Wibaut (1931), and Kjerrumgaard (1948).

Apart from these surveys, a great number of case reports of individual families exist, but few contribute anything of importance. Jackson and Linder (1953) described two affected sibs of a total of three, who had not only deafness with retinitis pigmentosa but also hypophosphataemic glycosuric rickets with a defect of renal tubular function. This finding is so unrelated to any other reports of Usher's syndrome, even the retinal degeneration being different in appearance, that it seems at least possible, especially as the parents were second cousins, that two distinct recessive syndromes were involved, neither of them being classical Usher's syndrome. The family of Roberto and Carbonara (1959) is also of some interest because of the suggestion that gonadotrophic and ovarian function is subnormal in members affected with typical Usher's syndrome. If confirmed, this suggestion may provide a clue to the nature of the inborn error of metabolism involved in the causation of this condition and may be of relevance to the findings in the families of Koennecke (1919) and Richards and Rundle (1959). In these families ataxia with peripheral muscular wasting is combined with underdevelopment of secondary sexual characteristics and mental deficiency. Progressive deafness in childhood is present but no retinitis pigmentosa. A metabolic block in steroid metabolism was detected by Richards and Rundle (1959).

While these two families do not belong to the classical syndrome of congenital deafness with retinitis pigmentosa, they do throw into sharp relief the complex and overlapping involvement of the ear, the eye, and the central nervous system in a very wide variety of genetically determined syndromes. Of this heterogeneous complex, described by Kufs (1927) and Hammerschlag (1932, 1933, 1934) as heredodegeneratio acustico-retinocerebralis, or heredopathia-acustico-optico-cerebrospinalis, retinitis pigmentosa with congenital deafness undoubtedly forms a distinct entity but it overlaps in many ways with other component and as yet ill-defined syndromes. Thus Hallgren (1959) showed that a large number of his cases of Usher's syndrome suffered from ataxia and, in addition, mental deficiency which was not due to lack of educational opportunity on account of sensory deprivation. Both he and Stenger (1956) concluded that the ataxia was due to a combination of vestibular and visual disturbances and not to any degeneration of the central nervous system. Steinberg (1937) and Arnvig (1955) have shown that, of all forms of hereditary deafness, vestibular disturbances are most common in Usher's syndrome. The mental deficiency does, however, indicate that a relation exists between this syndrome and other genetical conditions in which eye, ear, and central nervous system abnormalities in various combinations may be associated. These include, in addition to the condition described by Koennecke (1919) and Richards and Rundle (1959), dwarfism, retinal degeneration, and deafness (Cockayne, 1936) and deafness in the Laurence-Moon-Bardet-Biedl syndrome (Burn, 1950; Graf, 1964), Niemann Pick disease (Oppikofer, 1935) and juvenile amaurotic idiocy or cerebro-macular degeneration (Wibaut, 1931; Steinberg, 1937; Loebell, 1938) as well as several of the recessive syndromes mentioned in the introduction (Refsum *et al.*, 1949; Shaw and Duncan, 1958; Alström *et al.*, 1959). Furthermore, both visual and audi-

tory degeneration, either singly or in combination, are relatively common in the genetically determined cerebellar ataxias such as those of Friedreich (Matthews, 1950) and of Pierre Marie (Clauss, 1924; Vitello, 1939). It is of some interest that the heart is also often involved in this disease complex (Gordon and Hudson, 1959 (Refsum's syndrome); James and Fisch, 1963 (Friedreich's ataxia); Jeune, Tommasi, Freycon, and Nivelon, 1963).

The unitary concept of Hammerschlag (1932, 1933, 1934) is untenable as Albrecht pointed out in 1922 and 1941, basing his opinion both on genetical and pathological grounds. Though Albrecht went too far in claiming that every single component of the 'heredopathia acustico-optico-cerebro-spinalis' was inherited independently, it is equally clear that several genes giving rise to several recessive syndromes are involved, there being no basis for any estimate of the exact number. Bias introduced by the particular clinical interest of the observer is undoubtedly a factor making for additional heterogeneity which is more apparent than real. The main distinctive feature of the syndrome of deafness with retinitis pigmentosa is that the hearing loss is extremely early in onset or congenital, and frequently leads to profound childhood deafness, whereas it is usually later in onset and progressive, or even absent altogether, in the other component syndromes of this complex entity, which are, as a result, poorly represented in the socio-educational isolate of profound childhood deafness.

At the biological level, however, even this is not an absolute criterion of genetical heterogeneity, since it has been shown in the papers quoted on page 121 that the age of onset of deafness may vary considerably in different strains of recessively deaf mice, and that it is influenced to a large extent by the residual genotype, even when the main gene involved is identical. While many of the genes causing recessive deafness in mice are associated with disturbances of equilibrium, whether of vestibular or central origin, a strain described by van der Hoeve (1923), in which deafness was associated with a retinal dystrophy, has unfortunately not been reinvestigated with modern techniques. Even so, it is abundantly clear that many points involving qualitative and quantitative variations in the clinical expression of syndromes involving deafness in man may be profitably studied in analogous situations in laboratory mammals, a point that Hammerschlag (1932, 1933, 1934) emphasized, basing himself on a lifelong experience of the problem.

This clinical heterogeneity of the retinal, the auditory, and the neurological features of this complex is well illustrated by the thorough investigation of unselected cases of tapeto-retinal degenerations reported by such authors as Perrin (1958). The whole question is extensively reviewed in the books of Grimaud, Mounier-Kuhn, Gignoux, Martin, Paufique, Bonamour, Cordier, and Dureux (1962) on the association between troubles of the eye and ear, of Liveriero and Galli della Loggia (1962) on hereditary factors in oto-laryngology, and of Franceschetti, François, Babel, de Rouck, Dieterle, Forni, Klein, Ricci, and Verriest (1963) on tapeto-retinal degenerations.

Since the classical syndrome of retinitis pigmentosa with deafness is so well defined and was described so early in the course of the scientific study of profound childhood deafness, it has been recognized as a distinct clinical entity in most of the surveys, including those of the 19th century, mentioned above. As Hallgren (1959) points out, in adults, at least, it is easy to diagnose; and both Lindenov (1945) and Waardenburg (1956) describe marriages between persons with this syndrome and persons with clinically undifferentiated recessive deafness, whose children, though double heterozygotes, enjoy normal hearing. Fraser (1965a) has described a marriage between a man with deafness with goitre (Pendred's syndrome) and a woman with Usher's syndrome: their only daughter had normal hearing.

In children the diagnosis, without the benefit of electro-retinography, is sometimes difficult, as retinitis pigmentosa may not be detected ophthalmoscopically till adult life; nevertheless, many cases of Usher's syndrome appear in surveys of deaf schoolchildren (Henning, 1928, in Sweden; Lamy, Doll, and Marillier, 1949, in France; Arnvig, 1954, 1955, in Denmark; Diallinas, 1959, in Switzerland; Fraser, 1962a, 1964a, in Great Britain; and Danish, Tillson, and Levitan, 1963, in the U.S.A.). Because of these difficulties of diagnosis in children, however, the true prevalence of the syndrome may best be gauged in adult deaf populations, and Lindenov (1945) and Hallgren (1959) agree on an estimated incidence of 3 cases per 100,000 population in Denmark and Sweden respectively.

The Syndrome of Goitre with Deafness. There can be little doubt that Pendred's syndrome, i.e. the association of sporadic, as opposed to endemic, goitre with profound childhood deafness, is more common than Usher's syndrome. There can equally be little doubt that, despite the fact that Pendred wrote his original description of

two affected sisters in 1896 (Fig. 2), this condition has received very little attention until recently. Thus, though there are plentiful hints of its presence in surveys of deaf populations, both adults and children (Uchermann, 1901; Henning, 1928; Lindenov, 1945; Hopkins and Guilder, 1949; Arnvig, 1954; Wildervanck, 1957a) and also in case reports of individual families (Pendred, 1896; Brain, 1927; Deraemaeker, 1956; Thieme, 1957; Johnsen, 1958; Elman, 1958), it was not until 1960 that its true numerical importance as a component of the heterogeneous entity of profound childhood deafness was suspected (Fraser, Morgans, and Trotter, 1960).

Clinical Notes:

MEDICAL, SURGICAL, OBSTETRICAL, AND THERAPEUTICAL.

DEAF-MUTISM AND GOITRE.

By VAUGHAN PENDRED, M.R.C.S. ENG., L.R.C.P. LOND., LATE HOUSE SURGEON TO GUY'S HOSPITAL.

THE curious association of deaf-mutism and goitre occuring in two members of a large family has induced me to record these cases. Why this association? Perhaps some readers of THE LANCET may be able to throw some light on the cause of this combination of diseases: Absence of thyroid—cretinism; overgrowth of thyroid—deaf-mutism. I append the family history as recounted to me by the mother. The family is an Irish one, and the parents have been upwards of forty years resident in Durham. The father, aged sixty-six years, and the mother, aged sixty-seven years, are alive and healthy. They have had ten children, five sons and five daughters. In an epidemic of small-pox twenty-five years ago the whole family was attacked with the exception of the younger of the deaf-mutes, and four males and one female died, although all had been vaccinated, and that recently, as they were children. The remaining son and two of the daughters are healthy and vigorous. The first goitre case is the first-born of the family—a spare woman now aged thirty-eight years. She is deaf and can only mumble indistinctly; little care has been taken to educate her and so she is imbecile. The goitre is a large multilobular hard tumour, the greater part on the right side of the neck; from time to time she suffers from dyspnœic attacks. The growth was first observed after the small-pox—i.e., at thirteen years of age. The second surviving girl is now aged twenty-eight years, and is the fifth of the family; she is a small, spare, intelligent woman, her expression being in marked contrast to her sister's. She is not absolutely deaf and can mumble incoherently; her education has been attended to with so much success that she has been "in service." The tumour is larger than in the other case, but is of the same character; it has been growing for about fifteen years, and during the last year has caused both dyspnœa and dysphagia, which have become so urgent that I have sent her to-day to Newcastle Infirmary for operation.

Durham.

FIG. 2. Dr Vaughan Pendred's original description of the syndrome of deafness with goitre from the *Lancet* (1896), **ii**, 532. (By kind permission of the Editor.)

The reason for this comparative neglect is not hard to find. For many centuries restricted geographical foci, especially in high mountainous areas of the Alps, the Andes, and the Himalayas, have been described where endemic goitre was prevalent and accompanied by cretinism, idiocy, and deafness. The rare examples of Pendred's syndrome and the true relation of sporadic goitre with profound childhood deafness had been completely thrust into the background by being wrongly associated in investigators' minds with this relatively common association. It is clear, however, from the writings of Bircher (1883) and of Kocher (1892) that these unfortunate cretins, in one of their main foci of the 19th century (Switzerland), were not all necessarily deaf but could not speak because of their retarded mental state. A full discussion of these points is to be found in Fraser (1960), Trotter (1960), and Fraser (1965a). It is unlikely that any simple biological relation exists between Pendred's syndrome and the endemic association of deafness and goitre. In fact, this whole complex of endemic 'deafness' and/or idiocy cannot properly be included in the definition of profound childhood deafness and will not be discussed here further.

Brain (1927) first invoked the hypothesis ot recessive inheritance with regard to Pendred's syndrome. Furthermore, he clearly foreshadowed the later findings of Morgans and Trotter (1958) that the goitre was associated with an inborn error of thyroxine synthesis, and that it was only one of several such errors existing. Morgans and Trotter (1958) showed, in fact, that the defect of iodine metabolism involved in this syndrome was similar if not identical to that implicated by Stanbury and Hedge (1950) in the causation of one type of sporadic goitrous cretinism. This defect in the incorporation of inorganic iodide into organic form in the thyroid gland may be relatively easily demonstrated (Fig. 3), and has been confirmed many times in Pendred's syndrome (see Fraser, 1965a, for references).

The distinction between Pendred's syndrome and sporadic goitrous cretinism of the type of Stanbury and Hedge (1950) is not clear cut and may be due, in some cases at least, to quantitative rather than qualitative differences in the degree of block of thyroxine synthesis involved. Thus cases of Pendred's syndrome that border on clinical cretinism exist (Fraser *et al.*, 1960; Fraser, 1965a), and furthermore gross speech disturbances, which, in a mentally retarded individual, may well be due to undetected deafness, seem to be associated with this type of error in thyroxine synthesis but not

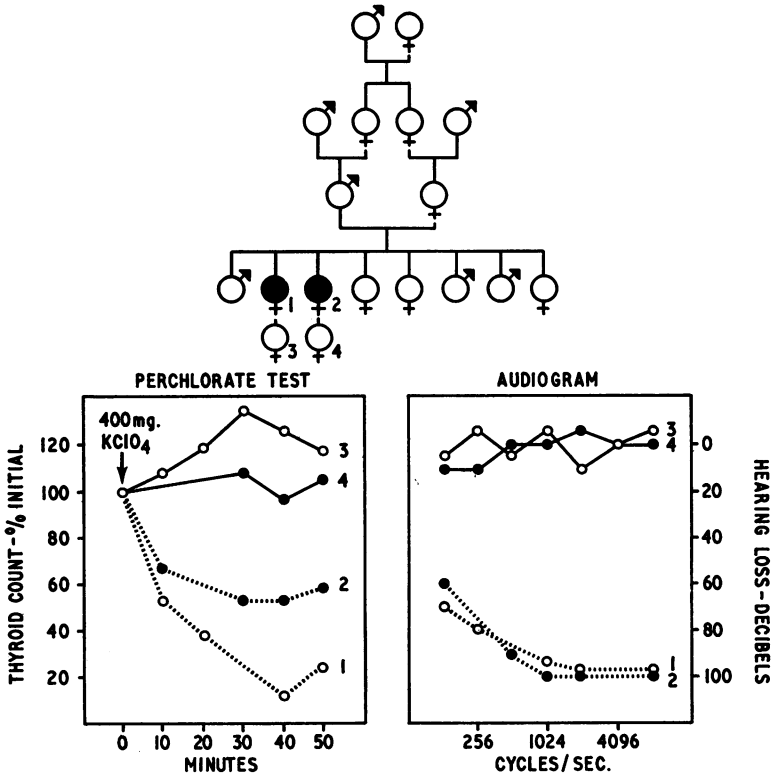

FIG. 3. Recessive inheritance of the syndrome of deafness with goitre in two sisters born of a marriage of first cousins (after Fraser *et al.* (1960), by kind permission of the Editor of the *Quarterly Journal of Medicine*). The response of the thyroid counting rate of the two sisters to $KClO_4$ given one hour after radioactive iodide is abnormal. The rate falls dramatically as iodide still in unbound inorganic form is discharged from the thyroid gland. The heterozygous daughters of the affected sisters show normal responses to $KClO_4$ and normal audiograms. The audiograms of their mothers show the typically greater loss of hearing in the high tones. ● indicates subject with Pendred's syndrome.

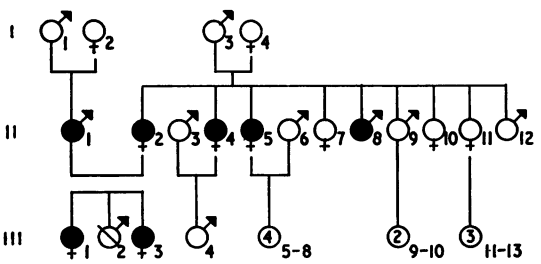

FIG. 4. This family was the subject of the paper of Jackson (1954) and was restudied by Fraser *et al.* (1960). The proposita, III.1, was in infancy thought to be a goitrous cretin of the type of Stanbury and Hedge (1950) but subsequently grew normally with thyroxine therapy, though she is profoundly deaf. Both parents (II.1; II.2) and her sister (III.3) are typical cases of Pendred's syndrome, as are three of her mother's sibs. Her brother (III.2) died in infancy and nothing is known of his hearing or thyroid state. Several marriages between persons both affected with Pendred's syndrome with, as expected, affected offspring have been ascertained by Fraser (1965a) as a consequence of a strong assortative mating tendency among the deaf (after Fraser and Trotter (1964), by kind permission of Masson et Cie, Paris.)

● indicates subject with Pendred's syndrome.

any other (for references see Fraser and Trotter, 1964; Fraser, 1965a). Sibships have been described (Fraser, 1965a) containing both euthyroid and cretinous individuals with Pendred's syndrome, and, indeed, such was the case in Pendred's (1896) original description (see Fig. 2). Furthermore, a re-analysis of a pedigree of Jackson (1954) (Fig. 4) shows that the same person may, at different periods, be diagnosed as a case of goitrous cretinism and of Pendred's syndrome. Fraser and Trotter (1964) describe a further family in which a female goitrous cretin with normal hearing has two aunts with typical Pendred's syndrome (Fig. 5). This family is of special interest in view of the possibility (Stanbury, 1963) that two genetically determined defects in the organic incorporation of iodide exist, only one of which also affects hearing. The proposita of Fig. 5 might then be a double heterozygote for these two genes which are non-complementary as far as thyroxine synthesis is

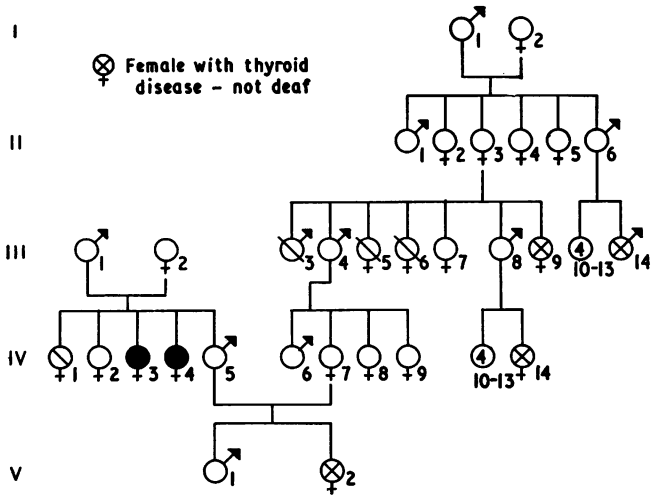

FIG. 5. The proposita, V.2, is a goitrous cretin of the type of Stanbury and Hedge (1950) but has two aunts (IV.3; IV.4) with typical Pendred's syndrome. She presumably inherited one mutant allele for Pendred's syndrome from her father and a different mutant allele from her mother. Hypothetically these two mutant alleles, whether at the same or different loci, are complementary as far as hearing is concerned but do not complement each other from the point of view of thyroxine synthesis. The mother's mutant allele seems to be expressed rather frequently in heterozygotes as is evidenced by goitre in herself and thyroid disease in several other members of her family marked with a cross (III.9; III.14; IV.14). (After Fraser and Trotter (1964), by kind permission of Masson et Cie, Paris.)

● indicates subject with Pendred's syndrome.

concerned but do complement each other from the point of view of hearing.

Whether one or two such genes exist, it is clear that there is considerable clinical overlap between Pendred's syndrome and goitrous cretinism. As a result, as in the case of Usher's syndrome, though probably not to such a great extent, some persons with Pendred's syndrome are mentally deficient because of inadequately compensated thyroid failure interfering with brain development in infancy. These are probably the only two common genetically determined causes of profound childhood deafness, which are specifically associated with mental deficiency, though occasionally a mistaken diagnosis in early life will lead to the lifelong confinement of a deaf person of normal intelligence in an institution for the mentally defective (Grewel and van den Horst, 1959a). Such mistakes, fortunately rare now, were frequent in the past and, indeed, until comparatively recent times, little attempt was made to differentiate between profound childhood deafness and mental deficiency.

The published reports on the association of deafness with goitre have been extensively reviewed by Fraser (1965a) in the course of a description of a personal series of 207 families with Pendred's syndrome. Taking into account the very wide clinical variation in the expression of Pendred's syndrome, which can often lead to difficulties in diagnosis, especially in children in whom the goitre has not yet developed, the author concludes that the prevalence of Pendred's syndrome is of the order of 7·5 cases per 100,000 births in the British Isles.

The Syndrome of Electrocardiographic Abnormalities, Fainting Attacks, and Sudden Death with Deafness. In 1957 Jervell and Lange-Nielsen described a family from Norway in which four of six sibs suffered from profound childhood deafness. All four had been subject from early childhood to curious fainting attacks, during which three had died at the ages of 4, 5, and 9 years. The only significant clinical finding that could account for this macabre phenomenon was that the deaf children showed very striking abnormalities of the electrocardiogram, undescribed previously and characterized by a gross prolongation of the QT interval (Fig. 6). Dr F. N. Wilson, who examined the electrocardiogram of a deaf child who died at the age of 13 with an identical condition (Levine and Woodworth, 1958), was so impressed by the tracings that he remarked, 'I am afraid you will have to place the ECGs in a group called "screwballs".' During a screening, using

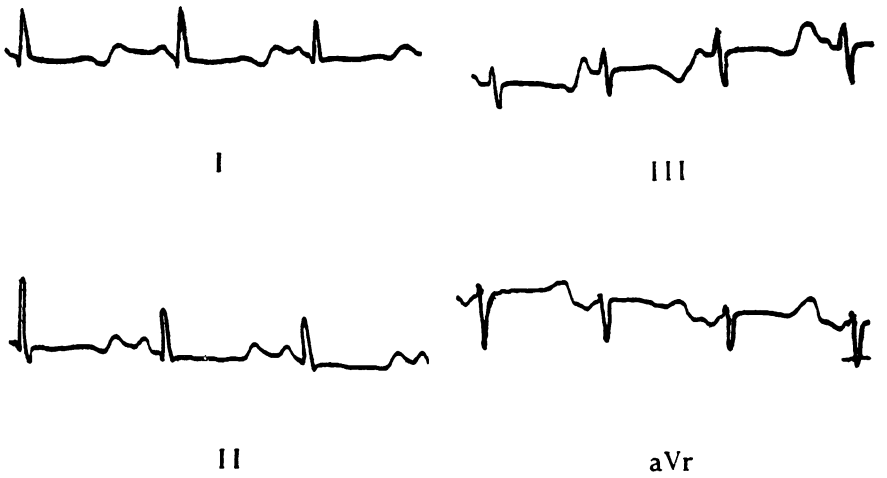

FIG. 6. Electrocardiogram (cardiac cycle = 0·80 sec.) of a case of the recessive syndrome of deafness with fainting attacks, electrocardiographic abnormalities, and sudden death. This tracing shows the distinctive features characteristic of this condition—the extreme prolongation of the QT interval and the bizarre, often biphasic, T waves (from Fraser *et al.* (1964a), by kind permission of the Editor of the *Quarterly Journal of Medicine*).

electrocardiography, of several thousand deaf people, both children and adults, 9 further cases of this condition were uncovered and described by Fraser, Froggatt, and James (1964a) and Fraser, Froggatt, and Murphy (1964b). These authors have suggested that this condition be called the cardio-auditory syndrome of Jervell and Lange-Nielsen.

Ward (1964), on the other hand, described a brother and sister with a very similar clinical and electrocardiographic picture but in whom there was no deafness. While the boy died at the age of 18 months before any definite pronouncement regarding his hearing state could be made, the girl is alive and at the age of 8 years has a normal audiogram. As in the cases of Usher's and Pendred's syndrome it seems as if closely similar conditions with and without deafness exist, the genetical relation between them, in the absence of the possibility of experimental breeding tests, being unclear. It should be noted, however, that the cardiac disturbance, both in Ward's (1964) report and in a similar one by Barlow, Bosman, and Cochrane (1964), seems to be dominant rather than recessive.

Morquio (1901) described a family of Uruguayan peasants, five of whose eight children had suffered from a series of fainting attacks; these attacks had begun at the age of 4 years and four of the children had died during them. Morquio studied two of these sibs, one of whom died in his wards at the age of 8 years. No cause of death was apparent at necropsy. The two boys were described as morose and unsociable and it is conceivable that these epithets cloaked a degree of undetected deafness. On the other hand, it may be that Morquio's family conforms to that of Ward (1964) without deafness rather than to that of Jervell and Lange-Nielsen (1957) with deafness. In either case there is little justification, in the absence of electrocardiographic documentation, for the claim sometimes made (Canabal and Dighiero, 1951) that the cases described by Morquio (1901) represent the first familial example of congenital heart block. Whatever the truth of the exact relation between these families, it is clear that a study of these syndromes has much to contribute to the tragic problem of sudden deaths in infancy and childhood, a proportion of which may be due to unsuspected cardiac metabolic defects of this type.

Even though the ECG was introduced as a routine tool of clinical investigation comparatively recently, it may be asked how the other features of this very striking condition escaped detection and characterization among the congenitally deaf for so long. Unfortunately, however, sudden death in children was until recently, and still is today in many parts of the world, a far too common phenomenon to attract much attention. Nevertheless, there is little doubt that Meissner's (1856) description fits the syndrome under discussion. He tells of a deaf girl, named Steinin, in the school for the deaf in Leipzig, who, while being reproached by the director for some trifling theft, fell down in

a faint and could no longer be revived. Her parents evinced no surprise when informed of her untimely end, for they had lost two children previously in a very similar manner.

The fainting attacks characteristic of this cardio-auditory syndrome of Jervell and Lange-Nielsen are sometimes compatible with survival to adult life, and there is some evidence that the severity of the cardiac lesion decreases towards the end of childhood (Fraser *et al.*, 1964a, b). In children the condition may be misdiagnosed as *petit mal* or even hysteria and the inclusion of a boy born of related parents with epileptiform attacks in the survey of Swedish schoolchildren by Henning (1928) and two children with fainting spells in the similar survey of Danish *et al.* (1963) in the U.S.A., indicates that this syndrome, though rare, has a widespread geographical distribution among deaf children.

Because of the high mortality of affected persons in infancy and childhood it is difficult to obtain any good estimate of the prevalence of this condition in the population at birth. After an exhaustive discussion of the problem of ascertainment, Fraser *et al.* (1964b) reached the conclusion that this true prevalence may be as high as 1 per 100,000 births, though the incidence among children of school age is a good deal less.

Other Recessive Syndromes Involving Deafness and the Pathogenesis of Recessive Deafness. Apart from the three conditions described in the preceding sections and the whole tangled pattern of the 'heredopathia acustico-optico-cerebro-spinalis', discussed in connexion with Usher's syndrome, many other distinctive accompaniments of profound childhood deafness have been described, often restricted to a single family but clearly inherited in a recessive manner. While these associations are likely to be due to the pleiotropic action of single abnormal genes in homozygous form, the possibility of the coincidence of two such abnormal genes by chance in several sibs cannot be excluded. Among these accompaniments are congenital absence of the tibia (Carraro, 1931), myoclonic epilepsy (Latham and Munro, 1937), and dystrophy of the nails (Feinmesser and Zelig, 1961). Yearsley (1934; 1935) also described a girl with nail abnormalities in the course of a survey of over 4,000 deaf schoolchildren in London.

In 1963 Wildervanck reported two sibs born of normal parents with ectrodactyly and profound childhood deafness. This combination had been described by Uchermann (1901) from Norway, and Kemp (1953) from Denmark, but in these cases, unlike those of Wildervanck, retinitis pigmentosa was an additional component. Wilhelmi (1873) mentions a deaf person with ectrodactyly in his survey of the deaf of the province of Magdeburg in Germany and Féré (1896) and Urbantschitsch (1910) also refer to the association, all without giving further details. While it is clear that this association of deafness with ectrodactyly cannot be regarded as a coincidence, especially since recessive inheritance of ectrodactyly is rare (Klein, 1932), it may of course sometimes occur fortuitously. Thus Yearsley (1934; 1935) describes a girl who had ectrodactyly, inherited in the usual dominant manner from her father, and whose deafness was acquired during an attack of meningitis in infancy.

It seems very probable that in many other families the association in some members of profound childhood deafness with other defects is fortuitous and due to independent segregation of two genes, one causing deafness and the second the other anomalies. Among such coincidental defects may be mentioned recessive dystrophia reticularis laminae pigmentosae retinae (Holmgren, 1950), dominant pulmonary stenosis (Lewis, Sonnenblick, Gilbert, and Biber, 1958), and recessive total albinism (Ziprkowski and Adam, 1964).

The involvement of profound childhood deafness as a component of a great many syndromes covering a broad spectrum of associated clinical lesions raises many basic biological problems. It is known that a variety of drugs and chemicals (streptomycin, quinine, arsenic, etc.) exert a toxic effect on the auditory apparatus. The marked selectivity of this effect may well be associated with the unique features of the VIIIth nerve, implicit in the relation of its end-organ to the endolymph.

Like intracellular fluids, the endolymph is rich in potassium (Citron and Exley, 1957). While the finer details are a matter for controversy, it is clear that this liquid is formed through a series of biochemical mechanisms of great complexity and it is very possible that its composition must be kept constant within rather narrow limits to maintain the hair cells of the VIIIth nerve in health and to ensure the propagation of sound. Thus quantitative or qualitative changes in endolymph composition might be expected to lead to degeneration of the membranous labyrinth and to deafness whose extent and rapidity of onset might be dependent on the nature and severity of the derangement involved.

It is clear also that recessive deafness of the type under discussion thus far is in fact due to degen-

eration of the membranous labyrinth and not to any gross malformation of the structures of the middle and inner ears. This point is elaborated further in a subsequent section on the pathology of deafness. Deol (1954), in discussing postnatal neural cellular degeneration (abiotrophy in the sense of Gowers (1902) and Collins (1919)) in the labyrinths of various types of recessively deaf mice, wrote as follows: 'It is probably correct to say that abiotrophy means the degeneration of cells due to purely chemical causes. There are many ways in which this may happen; they all have one thing in common; a chemical situation is revealed and localized by that type of cell which is most sensitive to the chemical change in question. This selective effect may be brought about by a shortage of a key nutrient; or by an increased demand for a key nutrient present in normal quantities; or by an increase of a biologically active metabolite; or by an increased sensitivity to such a substance present in normal quantities; or indeed in many other ways.'

As so little is known of the normal processes of the formation of the endolymph and of other features of the normal metabolism of neural cells in the labyrinth, it would be idle at this stage to speculate further. It is instructive in this context to note that 30 years after the discovery of phenylketonuria by Følling (1934), the relation between this inborn error of metabolism and the associated mental deficiency is still not understood. In the case of deafness, no clues of this sort are, as yet, to hand. It may well be, however, that in the future both the normal processes of health and the abnormal pathways involved in deafness will be unravelled and that the clinical associations of deafness in man will provide some useful clues to their elucidation. In addition, these syndromes are of importance in wider fields of medicine and human biology in that they are potentially capable of throwing much light on obscure aspects of normal and abnormal iodine metabolism and of the pathogenesis of sporadic goitre in general (Fraser, 1962b), of cardiac (Fraser *et al.*, 1964a) and of retinal metabolism, and of many other processes, reflected in the diversity of these syndromes. Nor is this list exhaustive, for there can be little doubt that further such clinical diversity will be revealed in the future and will eventually be correlated with the underlying inborn errors of metabolism. In the meantime a preliminary genetical segregation analysis of the data of Fraser (1962a, 1964a) concerning 2,355 deaf schoolchildren shows that presently unidentifiable recessive deafness is responsible for about 26% of the total or 26 cases per 100,000 births (assuming the incidence of profound childhood deafness to be 1 per 1,000 births (see page 145)). In this computation allowance is made for the cases of Usher's and Pendred's syndromes which cannot be diagnosed by clinical inspection in children (see pages 124 and 127).

While hereditary deafness which is due to malformation of the middle ears and is conductive

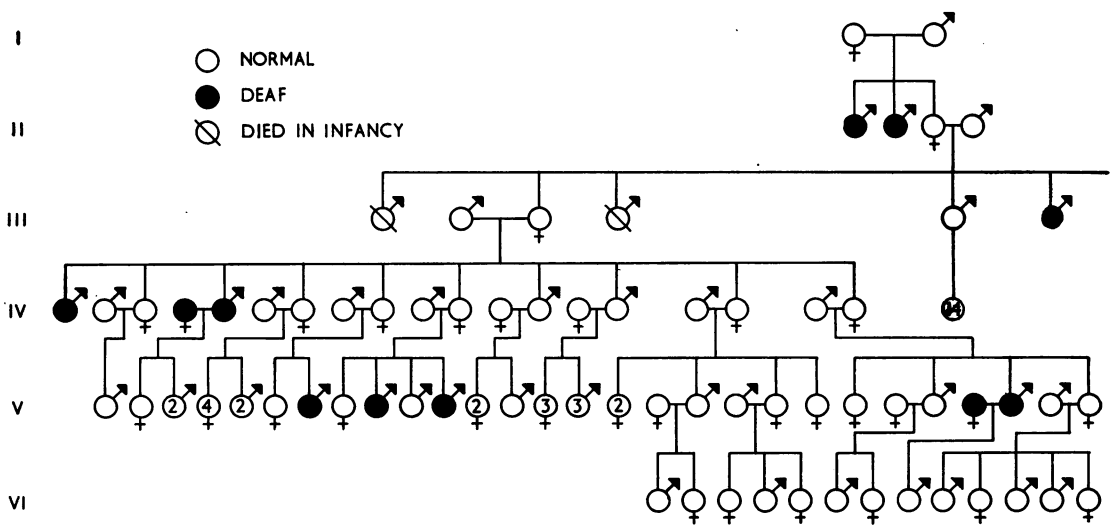

FIG. 7. Legend opposite.

rather than perceptive in character, usually follows a dominant mode of inheritance and will be discussed in a subsequent section on congenital malformations, one recessive syndrome involving such conductive deafness has been described. Cryptophthalmos is well known to be associated with a large variety of skeletal and visceral congenital malformations (Duke-Elder, 1952). Fraser (1962c) described two families containing four affected sibs, one of who was deaf due to malformations of the ossicles of the middle ear (see Fig. 10, page 138) and two of who had been born too malformed to be viable.

Such deafness was also a feature of the case of Gupta and Saxena (1962). It may well be that semi-lethal recessive syndromes of this type are due to a basically different genetical mechanism from the perceptive types of deafness described above. These latter are probably associated with inborn errors of metabolism which, in modern genetical theory, are due to single amino acid substitutions, impairing the function of essential proteins such as enzymes. Such substitutions are thought to be due to changes in a single base pair of the chromosome and do not usually lead to any clinical disturbance in heterozygous form. It may be that many mutations which often do cause overt clinical effects in heterozygous form (dominant inheritance) are due to changes affecting more than one base pair, even though such deletions, inversions, or other chromosomal rearrangements are too small to be detectable by conventional karyotype analysis. Complex recessive congenital malformation syndromes such as cryptophthalmos may then represent the homozygous state of such small chromosomal rearrangements. The pathways through which chromosomal rearrangements as a whole cause their effects are poorly understood, but it is probable that they differ radically from the modus operandi of inborn errors of metabolism.

Sex-linked Recessive Deafness. Kramer (1835) has already been mentioned in the introduction as one of the first of that remarkable group of investigators who placed the study of profound childhood deafness on a firm scientific footing. He gave an account of a sibship containing five hearing sisters and six deaf brothers born of normal parents and without any other deaf relations, though, since the family did not involve transmission from one generation to the next, he did not regard it as a bona fide example of heredity. Hints of the existence of sex-linked recessive inheritance may also be obtained from the sex distribution of deafness in the data of Wilde (1853) (see Fraser, 1965b, for an analysis), and Fay (1898) in his monumental account of 4,471 marriages in which one or both partners are deaf does include an account of a family in which two deaf brothers had a deaf uncle and nephew.

Much better defined examples of sex-linked recessive inheritance have been presented more recently, of which undoubtedly the most impressive is the pedigree of Dow and Poynter (1930) (Fig. 7). Other families in which the presumption of sex-linked inheritance is strong, though formal proof is impossible, have been described by Mitsuda, Inoue, and Kazama (1952) from Japan; Sataloff, Pastore, and Bloom (1955) from the U.S.A.; Parker (1958) from Australia; Deraemaeker (1958) from Belgium; Mohr and Mageröy (1960) from Norway; Livan (1961) from Italy; and Richards (1963) and Fraser (1965b) from Great Britain. Many other families in which deafness has been

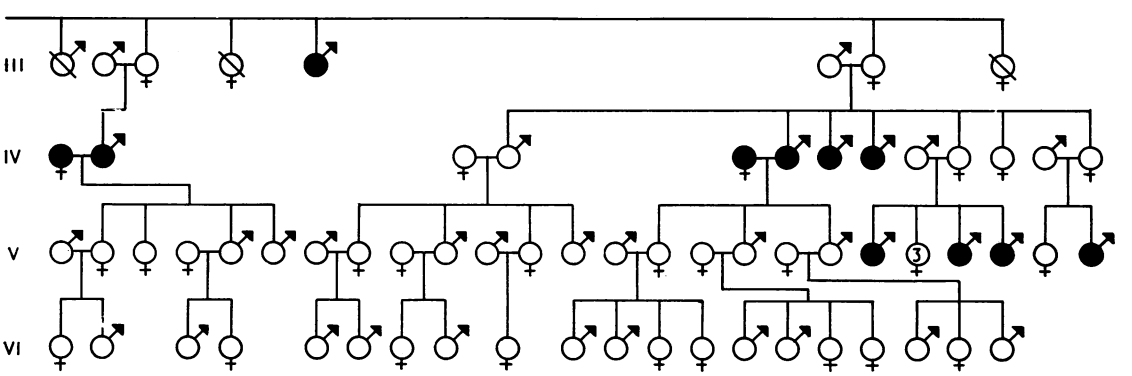

FIG. 7. Pedigree of sex-linked recessive deafness after Dow and Poynter (1930). (By kind permission of the Editor of *Eugenics Quarterly*.)

limited to one sex, either females (de Vido and de Stefani, 1952) or males (Cerri and Marcato, 1958), have also unfortunately and erroneously been described as examples of sex-linked inheritance.

Fraser (1965b) has shown by an analysis of the careful pedigree data of Hopkins and Guilder (1949) and of Stevenson and Cheeseman (1956) that sex-linked recessive inheritance plays a not insignificant numerical role in the causation of profound childhood deafness. He comes to the conclusion, based on his own material, that 6·2% of those cases of deafness in males, which are determined by simple Mendelian segregation at single loci, are due to sex-linked recessive inheritance and that males account for 51·7% of 1,228 such cases. The prevalence of sex-linked recessive deafness is about 3 cases per 100,000 males or about 1·5 per 100,000 births of both sexes. This figure is somewhat higher than the estimate derived by Chung *et al.* (1959) from various published surveys of deaf populations. It is of interest that the excess of males among cases of acquired profound childhood deafness in this series (Fraser, 1965b) is much greater, and males account for no less than 57·8% of 1,026 such cases, and an even greater proportion (61%) of 450 cases known to be acquired after the neonatal period. The reason for this marked excess propensity of males to acquire deafness as a sequel of meningitis or other diseases of early life is not clear. It was extensively discussed by Wilde (1853), Mygind (1894), Uchermann (1901), and Lindenov (1945), but no convincing explanation has yet appeared. This substantial excess of males among cases of acquired deafness may be observed in all other large series such as those of Shambaugh, Hagens, Holderman, and Watkins (1928) and Shambaugh, Hayden, Hagens, and Watkins (1930) from the U.S.A., and de Reynier (1959) from Switzerland.

Profound perceptive childhood deafness is often present in Hurler's syndrome (gargoylism) of the sex-linked, rather than autosomal, recessive variety (Herndon, 1954). While the clinical diagnosis of gargoylism is usually not difficult, chemical studies, both in life (Scheie, Hambrick, and Barness, 1962) and at necropsy (Jervis, 1950), have revealed typical derangements of mucopolysaccharide metabolism in persons who had not previously been clinically diagnosed as gargoyles. Thus it may well be that some cases of apparently uncomplicated sex-linked recessive deafness may be due to this disease (see also page 137).

Margolis (1962) and Ziprkovski, Krakowski, Adam, Costeff, and Sade (1962) have described, independently, a large family of Moroccan Jews living in Israel in which profound childhood deafness associated with partial albinism is clearly inherited in a sex-linked recessive manner. This family is unique in that, though this clinical association is well known, it is usually inherited in a dominant manner, one of several dominant syndromes involving deafness with pigmentary anomalies (see page 134). One of these is very similar to the association in the family under discussion and extensive pedigrees have been described by Tietz (1963) and Fraser (1965a, b). In these two families affected males have had four children (three affected girls, one normal boy), and sex-linked dominant inheritance is, therefore, a possibility. One of the families of Fisch (1959) may also fit this entity but unfortunately the sex is not noted.

Even if the hypothesis that dominant sex-linked inheritance is involved is accepted, the variability of the pattern of inheritance in this association of congenital deafness with partial albinism remains perplexing. One entirely speculative possibility is that the locus responsible for this syndrome is in fact on the X chromosome and that the mutant allele is usually expressed in females (sex-linked dominant inheritance). In some families, however, such as that of Margolis (1962) and Ziprkovski *et al.* (1962), the X chromosome which carries the mutant allele may undergo inactivation, of the type postulated by Lyon (1961), preferentially, perhaps because of some slight structural abnormality, giving rise to an appearance of sex-linked recessive inheritance. Alternatively, the mutant allele may be normally responsible for autosomal dominant inheritance but may have been translocated to one of the X chromosomes which again may have undergone preferential inactivation in carrier females in this family. It may be mentioned in this context that female heterozygotes in families exhibiting sex-linked recessive deafness of the usual variety without albinism enjoy normal hearing (Fraser, 1965b) and that no pedigrees of dominant deafness without pigmentary anomalies have been described in which apparent sex-linked inheritance has occurred.

Dominant Deafness with Pigmentary Anomalies. As the 19th-century writers on profound childhood deafness were extremely interested in all unusual clinical associations, it is remarkable that the very striking pigmentary anomalies which are now recognized as being relatively common among the deaf passed virtually unnoticed. Thus white forelock and partial albinism are unmentioned in the elaborate accounts of these painstaking

19th-century surveys. Even heterochromia of the irides which, in its specific association with deafness, takes a form with extreme contrasts between deep blue and rich brown hues is mentioned only in passing by Féré (1896) in an account of 'teratological stigmata of degeneration' among deaf children and by Wilhelmi (1873) and Uchermann (1901) in isolated cases, by the former in association with 'deep-set' eyes. At a later period heterochromia of the irides was noted in 4 of the 847 Swedish deaf children surveyed by Henning (1928).

Reports of isolated families and individuals showing an association of deafness with pigmentary anomalies also exist. As early as 1828 Hohl described a mother and two children who heard poorly and were fair with blue eyes while the father and three remaining children, with normal hearing, were darker with brown eyes. Some of the members of the famous Italian family, described by Rizzoli (1877) and Mazzini (1923), in which dominant inheritance of white forelock could be traced for at least eight generations suffered from profound childhood deafness. Urbantschitsch (1910) recognized that partial albinism, so called 'epicanthus', and heterochromia of the irides were associated with deafness, and Hammerschlag (1910) suggested that part of this complex might be inherited as a unit. Van Gilse (1926) reported an isolated case of partial albinism, heterochromia of the irides, and deafness. Mende, also in 1926, described a family in which dominant deafness of the type later defined by Waardenburg (1951) was segregating. It is interesting that Mende's family, like that of von Graefe (1858) (deafness with retinitis pigmentosa) and that of Kramer (1835) (sex-linked deafness), also originated from Berlin. Some of the members of this family showed partial albinism of the skin and hair, and the peculiar shape of the eyes gave a 'mongoloid' impression. Klein (1947) described an isolated case which belongs to the same complex, though with many additional abnormalities.

Waardenburg (1951) brought all these threads together and showed that a dominant syndrome existed, consisting of profound childhood deafness, partial albinism of skin and hair, heterochromia, total or segmental, of the irides, hairy overgrowth of the eyebrows, and a peculiar configuration of the eyes which he was able to show was neither due to epicanthus, nor related to that found in mongolism or hypertelorism, but a dystopia canthi medialis lateroversa (see Fig. 11, on page 138). This last feature, first clearly defined in two monozygous deaf female twins, who were restudied by Waardenburg, by van der Hoeve (1916), was that most constantly present in carriers of the mutant allele, whereas the other components were seen more irregularly. Even if the irides are not heterochromic, Waardenburg (1951), Bischler (1956), Diallinas (1959), and Fisch (1959) have remarked that they may often be of an unusual blue appearance with a hypoplastic stroma. Again, though profound childhood deafness is not invariably present in carriers, Waardenburg (1951), Fisch (1959), and Arnvig (1959) have pointed out that the deafness may be unilateral or of a milder degree, not causing serious disability.

Many case reports of Waardenburg's syndrome, as it is now generally called, have appeared since his classical description of 1951. For a time it was felt that there was some special relation between the syndrome and Holland and in fact many further cases were reported from that country (Keizer, 1952; Wildervanck, 1957b). Thus Partington (1959) stressed the Dutch ancestry of a large family with this condition from England, and Settelmayer and Hogan (1961) the lack of such ancestry in a family from the U.S.A. It is now clear, in fact, that no such special relation exists and that Waardenburg's syndrome exists among the deaf in all parts of the world. Reports have appeared of the effects of this condition in non-white people, in whom the characteristic white forelock, blue eyes, and patchy depigmentation of the skin are particularly striking (DiGeorge, Olmsted, and Harley, 1960; Scott and van Beukering, 1962; Calinikos, 1963, in Negroes; Zelig, 1961, in Jews of Indian ancestry; and Houghton, 1964, in a Maori boy). A very large family study covering 133 members of seven generations has been reported from Belgium by Delmarcelle and Pivont (1958). Waardenburg's (1951) syndrome has been described by Stoller (1962) from the U.S.A. in a boy in association with Sprengel's deformity of the shoulder.

Porot and Filiu (1959a) described it in association with epilepsy in an Arab boy from North Africa. The same authors (1959b) found an abnormal electroencephalogram, indicative of epilepsy, in a second case, who did not, however, suffer from any overt attacks. It is not at all clear what these findings indicate, though they may be related to the claim of Fisch (1959) that the skull structure of affected persons is abnormal. These abnormal EEGs cannot be regarded as coincidental since similar tracings were found independently by Grimaud *et al.* (1962) in two typical cases of Waardenburg's syndrome, neither of which had overt epileptic attacks.

Little is known of the EEG in profound childhood deafness in general. It is normal in the syndrome of deafness with electrocardiographic abnormalities (Fraser *et al.*, 1964a). Tracings have been obtained rather frequently in this condition because of the perplexing nature of the associated syncopal attacks. The EEG may be abnormal in the syndrome of deafness with retinitis pigmentosa (Grimaud *et al.*, 1962), which is not surprising in view of the associated involvement of the central nervous system discussed above.

It is clear (Fisch, 1959) that more than one syndrome associating dominant deafness with pigmentary anomalies exists. One such condition (Tietz, 1963; Fraser, 1965a, 1965b) has been discussed in connexion with sex-linked deafness. In this syndrome eye configuration is normal, whereas profound childhood deafness and partial albinism are constant features in carriers. Analogies exist between this syndrome and conditions occurring in other mammals. Thus while deafness is not found with recessive albinism in man or animals, it has been described in the dominant albinism of cats, sometimes associated, moreover, with heterochromia of the irides. Puybonnieux (1846), quoting earlier work of le Bouvier-Desmortier, wrote of a family of angora cats in which the mother was white and deaf while the father was black and white and hearing: all the kittens that were born white were deaf like the mother, while those that resembled the father were hearing. Deaf white cats are also mentioned by Darwin in his *On the Origin of Species* (1859) and subsequent works, and similarly affected dogs and rabbits are referred to by Klein (1947). While these animals seem to be totally albinotic, at least as far as the hair is concerned, deafness is associated in other mammals with genes causing spotting of coat colour, and this combination is also inherited in a dominant manner. One such gene is 'varitint-waddler' in mice (Cloudman and Bunker, 1945; Deol, 1954), and the same situation may occur in various breeds of dogs (Sorsby and Davey, 1954).

Various estimates have been made of the frequency of Waardenburg's syndrome among the deaf (Waardenburg, 1951; Wildervanck, 1957b; DiGeorge *et al.*, 1960; Partington, 1964). Fraser (1964a) found 56 cases associated with Waardenburg's syndrome and other pigmentary anomalies of the types discussed above in a group of 2,355 deaf schoolchildren. Assuming (see page 145) that profound childhood deafness affects 1 per 1,000 of the population, then the prevalence of such deafness due to these causes is about 2·5 cases per 100,000 births. Since, however, severe deafness is a relatively inconstant feature of Waardenburg's (1951) syndrome, the true incidence of this complex is undoubtedly much higher. There is no possibility in man of estimating the number of loci at which mutant alleles are responsible for these syndromes. Clinical differentiation is difficult because of the considerable overlap. Thus, while the partial albinism with deafness in the family of Ziprkovski *et al.* (1962) is distinguished by a sex-linked recessive mode of inheritance (see page 132), heterochromia of the irides is present as in Waardenburg's (1951) syndrome, though the configuration of the eyelids is normal. It could be that only one chromosomal segment is involved and that these different constellations of pigmentary anomalies, with and without deafness, are due to position effects caused by small chromosomal rearrangements.

These may not be detectable by present methods of examination, and Partington (1964) has, in fact, reported a normal karyotype in two typical cases of Waardenburg's syndrome. Ziprkovski *et al.* (1962), on the other hand, have described a possible abnormality of the X chromosome in one affected male. Pending confirmation, however, this finding must be interpreted with caution.

Dominant Deafness Without Pigmentary Anomalies. There can be little doubt that profound childhood deafness, without any association with disorders of pigmentation, can also be inherited in a dominant manner. It is strange that this has not been generally recognized earlier and, in fact, many investigators from Kramer (1835) to Stevenson and Cheeseman (1956) denied the possibility. In the earlier part of the 19th century deaf people were extremely handicapped economically and their fertility was, in consequence, very low (Mygind, 1892; Uchermann, 1901). Thus pedigrees in which deafness was transmitted for several generations did not exist. A possible exception is mentioned by Adams (1814), but his description is not clear.

The deaf, however, later overcame these economic handicaps, especially in the U.S.A., and proceeded to procreate to such effect that Bell (1883) entitled his monograph 'Upon the formation of a deaf variety of the human race'. The hypothesis of dominant inheritance can scarcely be avoided with reference to some of the families described by both Bell (1883) and Fay (1898) from the U.S.A. (Fig. 8), and this was in fact realized by Hammerschlag (1934). The tabulated results of Fay (1898) are even more striking, for the proportion of deaf offspring resulting from 599 marriages where

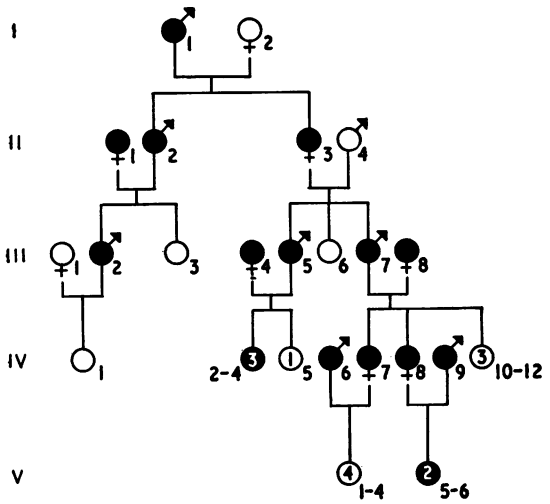

FIG. 8. Pedigree of dominant deafness in five generations after Fay (1898): I.1 is number 507 of that report. Recessive deafness is likely in the case of the deaf persons who married into the family (II.1; III.4; III.8; IV.6; IV.9.)

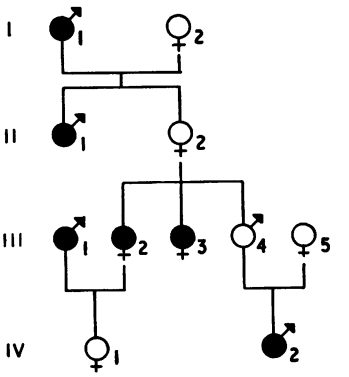

FIG. 9. Probably dominant deafness in the family of Mitchell (1863). Carriers who seem to be unaffected (II.2; III.4) may be relatively mildly, or unilaterally, deaf (see text).

only one of the partners was deaf was higher than that from 2,377 marriages where both partners were deaf (12·5% as opposed to 9·2%). As Bell (1883) pointed out, many hearing spouses of deaf persons may be related to them, or to other deaf people, and thus recessive deafness may be propagated in such marriages. On the other hand, it is clear that dominant inheritance is also of much importance in the transmission of deafness from one generation to the next.

More recently, in economically advanced countries, the fertility of the deaf has been approaching normal limits (Rainer and Deming, 1963) and, as their handicaps have been overcome, they have been tending to marry almost exclusively within their own community. Fay (1898) pointed out that marriages in which both of the partners were deaf were more likely, other things being equal, to result happily than those in which one of the partners was deaf and the other a hearing person. The formation of this isolate provides ample opportunity for the observation of genetically informative matings (see page 121). These points are discussed by Fraser (1964b), who gives several examples of dominant inheritance of profound childhood deafness with and without pigmentary anomalies.

Difficulties in the recognition of dominant deafness were compounded by a certain confusion between dominant adult perceptive deafness (progressive heredo-labyrinthine deafness of German speaking authors) and dominant profound childhood deafness which may well, in fact, be entirely different entities and also by the fact that carriers of the mutant alleles involved, as in Waardenburg's syndrome, may be unilaterally deaf, mildly affected, or even in some cases not affected at all. This is strikingly illustrated in a report of discordant uniovular twins with dominant deafness (Grewel and van den Horst, 1959b), one of who is profoundly deaf while one ear of the other is relatively spared, enabling him to follow normal schooling.

Bearing these points in mind, it is very likely that the pedigrees reported by Mitchell (1863) (Fig. 9) and Smith (1939) represent irregularly manifested dominant deafness. In the latter description, unilateral deafness was very common and transmitted through four generations, though two cases of bilateral profound childhood deafness also occurred. An 'obvious resemblance between deaf members' is mentioned and raises the possibility that in fact Waardenburg's syndrome is segregating in this family.

Everberg (1960) has studied unilateral deafness in schoolchildren very thoroughly in Denmark and finds it to be relatively common (185 cases in 182,934 children screened). He found that one such child belonged to a family in which Waardenburg's syndrome was segregating and another to a family in which cases of bilateral profound childhood deafness inherited in a dominant manner occurred. Johnsen (1954a, b), also in Denmark, studied a group of children who were handicapped by hearing loss but not to a sufficient extent to need education in a special school, and found, by family investigation, that a high percentage suffered from dominant deafness.

Chung *et al.* (1959), analysing the data of Stevenson and Cheeseman (1956) from Northern Ireland, first showed that a substantial proportion of the heterogeneous entity of childhood profound deafness was due to dominant inheritance. This conclusion was supported by Sank (1963). The data of these investigators combined with those of Fraser (1962a, 1964a) suggest that the proportion due to dominant deafness without pigmentary anomalies is of the order of 8–12%, including carriers of fresh mutations. There is no basis for an estimate of the number of loci involved but collectively they are therefore responsible for about 10 cases of profound childhood deafness per 100,000 births.

II: Deafness due to Involvement of the Ear in Congenital Malformations

The possibility has been discussed that the genetically determined profound perceptive deafness of childhood considered thus far may not be truly congenital but due to rapid and thorough disorganization of a normally developed acoustic mechanism. Such a possibility, if only hypothetical, has therapeutic implications for the future, by analogy with the present dietary treatment in infancy of such diseases as galactosaemia and phenylketonuria. Occasionally, however, as has already been seen in the case of the recessive syndrome of cryptophthalmos (see page 131), profound childhood deafness is truly connatal and primarily conductive in character, due to defects of the outer and/or middle ears.

It is of the utmost importance that such deafness be clearly defined for it is now remediable by operation, and the earlier in life detection and treatment take place the greater the chance of the acquisition of normal speech. Such deafness can easily be differentiated from perceptive deafness by systematic audiometry: usually, associated abnormalities of facial structure, which may be minimal, are sufficient for a diagnosis (Holborow, 1961). McKenzie (1958a) includes these various facial deformities in his concept of the first arch syndrome, suggesting that they have in common faulty embryonic development of structures derived from the first branchial arch. Though his claim, supported by Campbell, Campbell, and Swift (1962), that Waardenburg's syndrome forms part of this complex is unconvincing, the deafness being perceptive and the osseous structure of the ear intact (see page 144), at least two other dominant syndromes involving conductive or mixed congenital deafness, which fit this concept better, do exist.

Incomplete forms of the first of these were described by Berry (1889) and Collins (1900), and it is sometimes known as the Treacher Collins syndrome. It was thoroughly reviewed in a monograph by Franceschetti and Klein (1949), who showed that the complete syndrome, which they called mandibulo-facial dysostosis, consisted of abnormalities of the outer, the middle, and occasionally the inner ear, associated with antimongoloid palpebral fissures, coloboma 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 (Fig. 12). These deformities may occur in any combination and with varying degrees of severity; they may often be unilateral. Because of this marked variability, the mandibulo-facial dysostosis does not often lead to profound childhood deafness.

Many other associated deformities, of which the most common is cleft palate, may involve the skeleton and viscera of individuals with the mandibulo-facial dysostosis, and these are described in comprehensive reviews by Robbins (1963) and Maran (1964). It seems probable that only a proportion of cases which can be subsumed under the concept of the first arch syndrome are of genetical origin. While some of the large proportion of isolated cases may represent fresh mutations, others may be phenocopies. This is especially true of unilateral cases which often affect the outer and middle ear, usually on the right side and more often in males, with minimal or even no other facial deformities. Rare examples of dominant inheritance of such unilateral ear deformities are, however, known (Suzuki, Takaoka, and Hayasaki, 1960). Reports of the mandibulo-facial dysostosis in large family groups are rare, partly due to the large proportion of isolated cases mentioned above and partly to the fact that, because of the wide variability of clinical manifestations, some carriers of the gene responsible are virtually unidentifiable. Wildervanck (1960a) has, however, been able to follow the condition through four generations of a Dutch family.

Another branchial arch syndrome, which is distinct from the mandibulo-facial dysostosis, exists and is occasionally associated with profound childhood deafness. (It may have some affinities to the combination of fistula auris congenita, epibulbar dermoid, and auricular appendages described by Goldenhar (1952).) In this

syndrome the abnormal appearance of the face associated with the mandibulo-facial dysostosis is absent, though asymmetries of the outer ears, with occasional atresia, are found. Ear pits (fistulae auris congenitae), branchial fistulae, and pre-auricular appendages may also be present. Families demonstrating dominant inheritance have been described by Přecechtěl (1927), Fourman and Fourman (1955), and Wildervanck (1962). Aird (1946) mentions that ear pits are very commonly associated with deafness.

There is some doubt whether gross malformations of the cranium, also often inherited in a dominant manner, such as the dyscephalies, Apert's acrocephalosyndactyly, Crouzon's cranio-facial dysostosis, Vogt's cephalodactyly and dysostosis cleido-cranialis are associated with profound childhood deafness. Such an association is not mentioned in a monograph on these skull abnormalities by Nager and de Reynier (1948), though milder hearing loss is common. Profoundly deaf children with such malformations are described, however, by Love (1913) and Grimaud *et al.* (1962) and some are included in the series of Fraser (1964a). It seems unlikely that the association is fortuitous. It is not clear whether the deafness is conductive or perceptive but it seems that both may occur.

The coexistence of profound childhood deafness with the Klippel-Feil syndrome of malformations of the base of the skull and cervical vertebrae is certainly not coincidental. Cases, almost invariably females, sometimes with retraction of the eyeball, abducens paralysis, and other associated facial abnormalities, have been reported by Wildervanck (1952), Franceschetti and Klein (1954), Bardadin and Siedlanowska (1955), Wildervanck (1960b), Everberg, Ratjen, and Sørensen (1963), Whetnall and Fry (1964), and Fraser (1964a) (Fig. 13). It seems that the deafness in this condition is perceptive in character and radiological abnormalities of the inner ear have been demonstrated in several of these reports. There is no obvious simple hereditary pattern.

Many intermediate forms exist between these various malformation syndromes and precise diagnosis is often difficult; in some cases a malformation of the middle ear or bony labyrinth may not even be detected as being responsible for deafness. In common with the majority of other congenital malformations, the role of heredity is not always clear, though some relatively well-defined dominant syndromes exist. Though chromosomal rearrangements, too small to be detectable by present methods, may be associated with these conditions, it is perhaps surprising that the auditory apparatus is not systematically involved, in the absence of overt gross malformations of the outer ear, occasionally present in the D and E trisomy syndromes, in any abnormalities of the karyotype. Claims to the contrary, such as those of Patau, Smith, Therman, Inhorn, and Wagner (1960), based on cursory tests of hearing in infants with gross mental defect, cannot be accepted without much more painstaking investigation of the few survivors of infancy affected with this D (13–15) trisomy syndrome.

Chromosome studies in profound childhood deafness are somewhat sparse. Normal karyotypes have been reported, as is to be expected, in the recessive syndrome of deafness with goitre (Fraser, 1965a) and in the sole survivor of the sibship with the recessive syndrome of deafness with electrocardiographic abnormalities described by Jervell and Lange-Nielsen (1957) (A. Jervell, personal communication). A normal female karyotype was also found in the girl of Fig. 10 with the complex congenital malformation syndrome of cryptophthalmos (Fraser, 1962c), despite some uncertainty regarding social sex, and also in one of the girls with Klippel-Feil syndrome and deafness of the series of Fraser (1964a). Normal karyotypes have been recorded in the mandibulo-facial dysostosis (Maran, 1964) and in Waardenburg's syndrome (Partington, 1964 (see page 134)).

It has been suggested (Féré, 1896; Brunet, 1956) that congenital malformations are especially common in profoundly deaf children and are stigmata of a general associated degeneration. In view of the very wide spectrum of causes adumbrated in this review, it seems very unlikely that such a generalized tendency exists. In a survey of 2,355 deaf schoolchildren, Fraser (1964a) found 56 in whom the deafness was associated with congenital malformations of the types discussed here, as well as some hitherto undescribed varieties. In 6 of these 56, the operation of simple Mendelian inheritance could be detected from the family history. In some other cases the presence of sex-linked recessive gargoylism, of a clinically mild variety (see page 132), was suspected. In such children, the skull deformity and deafness are not congenital but progressive in infancy. The 56 cases included 19 (17 girls, 2 boys) with the Klippel-Feil deformity. In a proportion of the remaining 37 children a conductive element of the deafness, associated with malformation of the middle and/or outer ear, was detected. The prevalence of such malformation syndromes involving deafness may therefore be estimated at 2·5 cases per 100,000 births.

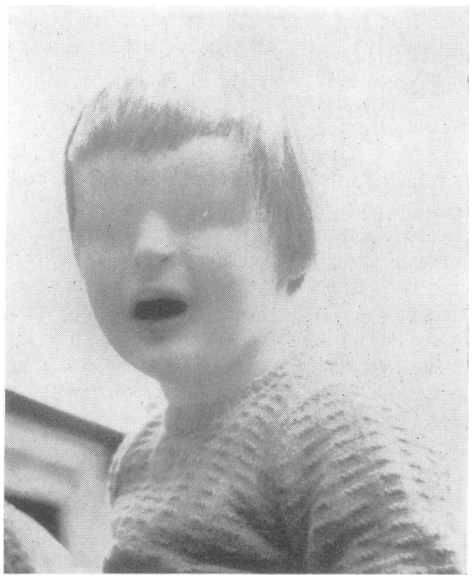

FIG. 10. Recessive cryptophthalmos with outer and middle ear malformations leading to conductive deafness.

FIG. 11. Waardenburg's (1951) dominant syndrome. This child shows the white forelock and dystopia canthi medialis lateroversa. The deafness is perceptive in character due to lesions of the membranous labyrinth.

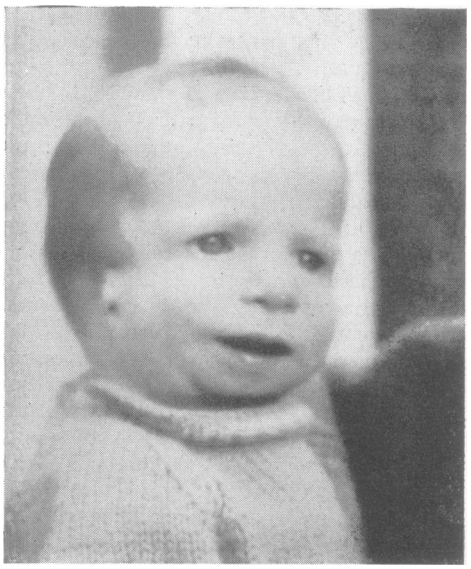

FIG. 12. Dominant mandibulo-facial dysostosis. The deafness is predominantly conductive in character but may be mixed.

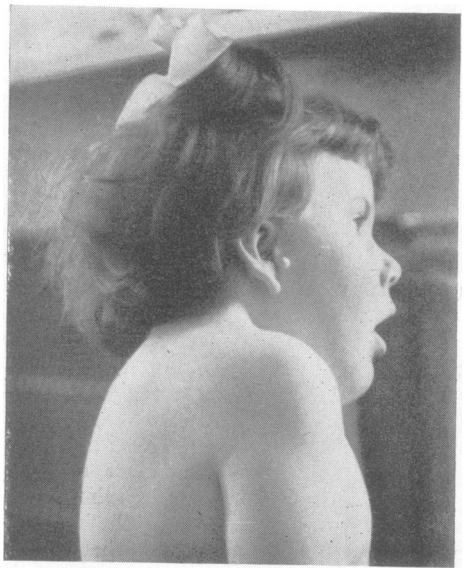

FIG. 13. Klippel-Feil syndrome with pre-auricular tubercle. The deafness is perceptive and associated with malformations of the bony labyrinth.

FIGS. 10–13. Malformations affecting the head associated with profound childhood deafness.

III: Acquired Deafness

Causes Acting in Prenatal Life. Of all acquired causes of deafness, those operating in foetal life may most readily be confused with genetical causes. The human mind abhors the unknown, and it is particularly easy to inculpate events of a distant and dimly remembered pregnancy for the family tragedy which the diagnosis of deafness in a child provokes. Some such causes are clearly factitious, ranging from the 'pium desiderium peculiare gravidae' of Wilhelmi (1873) to the permanent wave, sometimes invoked by modern mothers; others, such as congenital syphilis and toxoplasmosis and maternal rubella, are well substantiated.

Exaggerated claims have, in fact, been made for all these infections. Thus, though congenital syphilis was undoubtedly more important as a cause of deafness in the past than it is in most countries today (Love, 1913), it could hardly have been responsible for the ravages ascribed to it by de Parrel and Lamarque (1925) who considered it as the aetiological factor in almost all cases of profound childhood deafness. Again while congenital deafness due to toxoplasmosis is well documented (Kelemen, 1958, from the pathological, and Feinmesser and Landau, 1961, from the clinical viewpoint), the claim of Theissing and Kittel (1962) that it is responsible for 10–20% of all profound childhood deafness is entirely unconvincing. It is far more likely that the high proportion of positive reactors in toxoplasmosis tests, which these authors found among deaf children as opposed to hearing controls, is an acquired phenomenon associated with the institutional life which the former lead, predisposing to early infection with toxoplasma. In any case, it cannot be sufficiently emphasized that positive tests, whether for toxoplasmosis, rubella, or syphilis in postnatal life cannot be accepted as unequivocal evidence of the prenatal aetiology of deafness, but only as circumstantial evidence which has to be fitted into the remainder of the disease picture. Thus Burkinshaw, Kirman, and Sorsby (1953) were quite unable to correlate positive tests for toxoplasmosis with the clinical features of mental retardation in a study of 698 mental defectives in an institution.

Since the first description by Gregg (1941) of the association of congenital cataracts with congenital heart disease due to maternal rubella and the demonstration by Swan, Tostevin, Moore, Mayo, and Black (1943) that deafness could also be a component of this entity, the literature on rubella embryopathy has swelled to vast proportion. There is no doubt that Gregg (1941) did not in fact observe a new disease, though this does not in the least detract from the merit of this classical paper. Cases born in 1930 and 1936 were described by Beswick, Warner, and Warkany (1949) and suggestive earlier accounts exist of a boy with deafness and congenital cataracts (Wardrop, 1813) and another with deafness and congenital pulmonary stenosis (Leuch, 1892). Furthermore, cataract was a not uncommon accompaniment of deafness in surveys of ocular abnormalities among deaf children discussed on page 122 in connexion with retinitis pigmentosa (Adler, 1876; Lee, 1883). The epidemiological surveys of Lancaster (1954) covering Iceland, New Zealand, and Australia have also shown that increased numbers of births of deaf children occurred following rubella epidemics from 1898 onwards. Again Ivstam (1951) gives convincing details of an increase of deafness in Sweden following the rubella epidemics of 1936–7.

One of the lesser known features of rubella embryopathy is a widespread retinal pigmentation, often restricted to the peri-macular area, not interfering with visual acuity. This was mentioned by Gregg (1941) in two of his patients in whom the cataract was restricted to one eye, and was well described by Marks (1946), Bourquin (1948), and Emerson (1958). This retinopathy in deaf children without cataracts is a useful pointer to the aetiology of the deafness (Fraser, 1962d), especially in cases when, as may often happen, the mother is not aware of a sub-clinical attack of rubella in pregnancy. Other corroboratory features, indicating a diagnosis of rubella embryopathy, are a low birth weight and the season of birth corresponding to the seasonal incidence of rubella (Fraser, 1962d). In the western hemisphere most such births take place between October and March.

There can be little doubt that the 'new syndrome' described by Diallinas (1959), Amalric (1960), Amalric and Bessou (1962), Grimaud *et al.* (1962), and Remky, Klier, and Kobor (1964), of a primarily peri-macular tapeto-retinal degeneration, affecting 6–12% of children with profound deafness, is in fact rubella embryopathy. A consideration of the dates of birth, when given by these authors, is revealing in this respect. Fraser (1964a) found a similar incidence of this retinal lesion in a series of 2,355 deaf schoolchildren and, making use of all the diagnostic criteria mentioned above, combined with information from the mother, came to the conclusion that 133 (5·6%) owed their deafness to rubella. These children were seen in 1960–1 and do not include those rendered deaf during the

rubella epidemic of 1940. At that time the proportion of children deaf due to rubella was much higher (Martin, 1946).

The rubella virus does not attack only the eye, heart, and ear but is a generalized disease of the embryo. Dental deformities and microcephaly have been described in rubella children, as have generalized slight physical and mental retardation. The peculiar behaviour pattern and facial appearance of these children is well known to teachers of the deaf and blind. It is of interest that Grimaud *et al.* (1962) found abnormal EEGs in all 22 of their cases of deafness with retinal degeneration of the rubella type whom they tested.

Excellent reviews of the problem of the relation of virus diseases, especially rubella, in pregnancy to congenital malformations are provided by Kuntzel (1952) and Rhodes (1961). It may be said that no other virus has been conclusively incriminated as far as deafness is concerned. In particular, Heider (1934) in the U.S.A. and Candiotti (1949) in France showed that the 1918 pandemic of influenza did not cause any deafness among the offspring of affected pregnant women, though the epidemiological data of the former author might be interpreted as indicating that some acquired deafness due to infection in infants may have occurred.

The results of two prospective investigations of maternal rubella in the first twelve weeks of pregnancy (Manson, Logan, and Loy (1960) from England, and Barr and Lundström (1961) based on smaller numbers from Sweden) concur in estimating the risk of the incidence of hearing loss in the offspring at about 20%, of which a third is of sufficient degree to constitute a severe handicap. These facts are now generally well known and an interesting result is that occasionally women will adduce a fictitious attack of rubella in pregnancy to explain deafness in their child because of their anxiety to avoid the supposed stigma of an unknown cause.

Occasionally other possible prenatal causes of deafness are proposed. Since many drugs are known which cause postnatal deafness, there seems little reason to doubt that congenital deafness may sometimes be caused by unwisely large doses of such drugs, of which streptomycin is an example (Leroux, 1950; Kern, 1962), given to pregnant women. Then again, foetal malformations due to thalidomide may include aplasia or hypoplasia of the entire auditory apparatus (Rosendal, 1963). Such mishaps are rarities, however, and there is no evidence that profound childhood deafness on any large scale is due to such mechanisms. Thus Winckel (1948) has pointed out that, though a few cases of congenital deafness due to administration of quinine to pregnant mothers have been reported, there was no systematic increase of deafness prevalence in the Southern as opposed to the Northern States of the U.S.A., though quinine was extensively consumed as an anti-malarial drug in the former.

Finally suggestions have been made that endocrine diseases of the mother, such as pseudohypoparathyroidism (Hinojosa, 1958) and diabetes mellitus (Jørgensen, 1961) may predispose to congenital deafness in her children. Such occurrences, if they exist at all, must be very rare. Rubella is the only substantial known cause of prenatally acquired deafness today in countries with a high standard of medical care; the possibility cannot, of course, be excluded that other, as yet unsuspected, causes exist.

Causes Acting in the Perinatal Period. Misfortunes in the perinatal period account for many severe handicaps in children, and this applies no less to deafness than to blindness, mental deficiency, and spasticity. In fact, since the causative mechanisms are sometimes the same, it is not uncommon for two or more of these defects to be present together. Thus severe neonatal jaundice due to rhesus incompatibility, formerly fatal in most cases, caused deafness with various neurological and mental defects, especially in the first years of treatment (Crabtree and Gerrard, 1950). This damage is thought to be caused by a direct toxic effect of high bilirubin levels on the brain, the deafness being due not to involvement of the peripheral auditory apparatus, as in the types discussed thus far, but of the cochlear nuclei.

Apart from rhesus incompatibility, perinatal causes of deafness preferentially involve the premature child. The biology of prematurity is exceedingly complex, and many factors, both genetical and environmental, are involved in its causation. The especial hazards that the premature child faces in adapting to the extrauterine environment may lead to deafness in several ways. Thus immature liver function may cause difficulties in the conjugation of bilirubin and profound jaundice as in rhesus incompatibility (Crosse, Meyer, and Gerrard, 1955). Immature kidney function may lead to difficulties in the excretion of ototoxic drugs such as streptomycin and dihydrostreptomycin and the consequent high blood levels of these drugs may exert a particularly deleterious effect on the auditory apparatus of the premature newborn (Fraser, 1961; Marcus, Small, and

Emanuel, 1963). Finally birth trauma may lead particularly easily to haemorrhages from immature blood vessels and capillaries (Dollinger, 1927). The possibility of deafness being due to such haemorrhages in the inner ear was explored by Voss (1923) and Albrecht (1930), and the particular predisposition of the premature child was mentioned. It is likely that neonatal attacks of asphyxia, again especially common in premature children, aggravate this process, though it is also possible that the attendant anoxia has a specifically deleterious effect on hearing. That hearing is often involved in the generalized central nervous system damage due to birth injury, described from the anatomical viewpoint by Schwartz (1927), is demonstrated by the finding of Fisch (1955a) that a high proportion of children with cerebral palsy have significant hearing loss. Conversely Fraser (1964a) found neurological evidence of birth injury in 24 out of 2,355 deaf schoolchildren. Anoxia and/or birth injury may of course also, though less often, be responsible for deafness in normally mature children.

It is not easy to define exactly the various disturbances of the normal transition between the intra- and extrauterine environment that may preferentially affect the premature child. Such mechanisms may be responsible for the excess of premature children among those deaf due to unknown causes about who no convincing history of profound jaundice, drug administration, or gross birth injury can be elicited (Johnsen, 1952; Barton, Court, and Walker, 1962; Fraser, 1962a, 1964a), though it must be remembered that records of unfavourable perinatal events may be lost, forgotten, or otherwise unobtainable. The only known prenatally determined cause of deafness which is often associated with prematurity is maternal rubella, and it is possible, therefore, that unsuspected foetal infections, whether with the rubella virus or with other organisms, account for part of this excess. Johnsen (1952) points out that deafness of unknown aetiology affects especially firstborn premature children and the firstborn of twin pairs, both these groups being especially liable to difficult births. Twins are, in addition, frequently premature and their perinatal difficulties have the interesting and confusing consequence that subsequent concordance and discordance with respect to deafness are largely unrelated to zygosity.

Thus some deafness of unknown aetiology, especially in premature children, may be ascribed to difficulties in the adaptation, in the widest possible sense of the word, of the auditory mechanism of the newborn child to the extrauterine environment. The possibility cannot be excluded that such additional difficulties, affecting metabolic processes involved in the auditory pathway, may exist, of whose nature nothing as yet is known. The data of Johnsen (1952), Barton *et al.* (1962), and Fraser (1962a, 1964a) suggest that not less than 10% of profoundly deaf children owe their deafness to such misfortunes occurring in the perinatal period.

Causes Acting After the Perinatal Period. Deafness acquired through disease in childhood does not often cause confusion with genetically determined forms, though an important source of bias is introduced by the tendency, discussed above, of parents to seek for an explanation of the deafness of their child. Thus, in analyses based on the parents' story, measles and whooping cough have been invested with an importance that is totally disproportionate to their very small actual role, for these are diseases through which many children pass by the age that parents realize that speech development is seriously retarded. In the past otitis media was a common sequel of these diseases, and of scarlet fever, and often caused serious disability; profound childhood deafness due to otitis media is a rarity in economically advanced countries today.

In such countries meningitis is undoubtedly the most common cause of profound childhood deafness, acquired after the end of the neonatal period, and recently a very important numerical role in causation has been played by tuberculous meningitis. This disease, formerly almost invariably fatal, often left survivors with serious neurological sequelae, including deafness, in the first years after effective treatment was introduced. As in the case of the improved treatment of rhesus incompatibility, such iatrogenic disasters are much rarer today. This applies also to deafness caused by ototoxic drugs. Their mode of action is problematical but ototoxicity is determined at least to some extent by idiosyncratic reactions of the patients, partly under genetical control, and familial streptomycin deafness has been described (Horiguchi and Moiyama, 1957). Such phases in the advance of medicine produce very interesting secular variations in the spectrum of causes of deafness and there can be little doubt that acquired deafness, especially that due to childhood disease, will in fact cease to be of great numerical importance in the near future, since, with prompt treatment and the judicious use of ototoxic drugs, there is no reason why even meningitis should be followed by destruction of hearing.

There is a great excess of males (up to 60%) among those deafened by childhood disease. This was noted especially by Uchermann (1901), who discussed the great increase of deafness due to epidemics of cerebrospinal meningitis in the last century; this was apparent in the American data of Bell (1883), those from Denmark of Mygind (1892), his own from Norway, and many others. The reason for this increased predisposition of males is not clear, but it applies also in the case of a disease of infancy, first described by Voltolini (1882) and called by him otitis labyrinthica seu intima. This disease runs a far milder course than meningitis, though the two may be confused, but it frequently leaves deafness in its wake. The exact status of this nosological entity is problematical, though it may well bear some relation to the loss of hearing due to virus infections, sometimes complete and bilateral, which has been described in adults and older children by van Dishoeck and Bierman (1957) and Dawes (1963). Escudero (1948) in Spain ascribed a very important numerical role in the causation of profound childhood deafness to this entity. While his claim is in all probability exaggerated, that of Claverie (1956) that deafness due to such a cause is an extreme rarity probably errs on the side of excessive caution.

A large excess of male deaf children in the group of unknown aetiology (Fraser, 1965b) is very suggestive in this respect, and there can be little doubt that 'Voltolini's disease' and other unrecognized acquired causes play a substantial role in profound childhood deafness. Basing his estimate on such considerations, Fraser (1965b) comes to the conclusion that about 30% of 2,355 deaf schoolchildren owe their disability to acquired causes operating after the end of the perinatal period. Of this total no less than 105 are deaf following tuberculous meningitis.

It cannot be too strongly emphasized that these figures refer to the British Isles in 1960–1 and that the proportion may be very different in other countries. Thus even in comparatively prosperous countries, such as Poland, bacterial dysentery, typhoid, and diphtheria are still considered to be important causes of deafness in childhood (Bystrzanowska, Kuś, Osuch, and Wojnarowska, 1960), while in parts of Africa epidemic cerebrospinal meningitis still poses a vast problem.

IV: Otological Features of Profound Childhood Deafness

Profound childhood deafness has until recently been primarily the concern of educators rather than otologists. This situation is now changing, however, and otological investigations of the characteristics of the lesions involved are being undertaken with increasing frequency. The perceptive rather than conductive nature of the deafness in the vast majority of cases is well documented, despite McKenzie's (1958b) nonconformist claim to the contrary, and Secrétan (1953) and Fraser (1965a) have localized the lesion to the cochlear hair cells of the VIIIth nerve in certain types of recessive deafness.

A beginning has been made on the important problem of the correlation between audiometric pattern and aetiology of deafness by Fisch (1955b). The flat pattern, characteristic of rubella deafness, is ascribed to an interference with normal maturation affecting the entire organ of Corti. The retention of hearing in the low tones to a greater or lesser extent (Fig. 3) in recessive deafness (Hallgren, 1959; Fraser *et al.* 1964a; Fraser, 1965a) may be connected with the fact that the postnatal degeneration of the organ of Corti in recessively deaf mice (Deol, 1956b) usually proceeds from the base to the apex, the apical part being responsible for the transmission of low tones. This type of audiogram is often also found in Waardenburg's (1951) syndrome (Fisch, 1959), though in dominant deafness as a whole a flatter pattern is common (Wildervanck, 1953; van Egmond, 1954). In sex-linked recessive deafness, too, retention of some hearing at all frequencies is common (Fraser, 1965b).

There can be little doubt that similar audiometric patterns occur, as is to be expected, in members of the same family, affected with genetically determined deafness, despite the intervention of many secondary environmental factors such as trauma, noise, infection, and ageing. These similarities were clearly demonstrated by Ciocco, Hughson, and Palmer (1939) and are also apparent from the audiograms of Fisch (1955b) and Wildervanck (1957c). Very striking similarities were described by Parker (1958) in members of a large family with sex-linked recessive deafness.

No significant hearing loss has been described in heterozygotes for recessive deafness in man, whether autosomal (Wildervanck, 1957c) or sex-linked (Fraser, 1965b). Even double heterozygotes for two types of recessive deafness are unaffected (see page 124). A possible exception is a woman in pedigree 234 of the Clarke School Studies (Hopkins, Macklin, Mann, and Whitney, 1946; Hopkins and Guilder, 1949). Both her parents were deaf and had deaf sibs but hearing parents. She herself had four older hearing sibs

but was hard of hearing from infancy. Deafness of late onset in some double heterozygotes in mice has already been mentioned on page 121.

It is generally recognized that the audiogram cannot provide conclusive evidence of the aetiology of deafness in the individual case. At best it provides circumstantial evidence that can be used in conjunction with information derived from other sources in arriving at a putative diagnosis. There are so many exceptions to Langenbeck's (1936) law of symmetry (identical or very similar hearing loss in the two ears in inherited deafness, dissimilar in acquired) that it is virtually useless. It may, however, be said with some confidence that, if in a normally intelligent child, no response at all takes place at maximum intensities of the audiometer over the whole frequency range, then the deafness is likely to have been acquired.

Nor can the claims made in favour of vestibular function tests in the differential diagnosis of the cause of deafness be said to have been substantiated. While it is true that reduction of vestibular function is more common in postnatally acquired than in hereditary deafness, the survey of Arnvig (1955) showed that this difference between the two groups is only relative rather than absolute, as had previously been claimed. Furthermore, vestibular disturbances are extremely common in some genetically determined syndromes, such as that of deafness with retinitis pigmentosa (see page 123). Müller (1936) described disturbances of vestibular function in four members of a family with dominant profound childhood deafness, and Stoller (1962) reported complete absence of response to caloric stimuli in a boy with Waardenburg's (1951) syndrome. Much remains to be done in the otological investigation of profound childhood deafness. It is to be expected that systematic study of VIIIth nerve function in combination with thorough clinical and genetical appraisal can help considerably in arriving at a diagnosis of the cause of deafness in the individual case.

V: The Pathology of Profound Childhood Deafness

Despite the fact that those with profound childhood deafness do not usually die of this condition and, therefore, only infrequently die in circumstances of which pathologists interested in the ear are aware, and despite the difficulties of producing good histological preparations of the inner ear without intravital staining, a vast number of publications regarding the appearances of the auditory apparatus in profound childhood deafness are available, especially in the German language. Many excellent reviews of the subject have been written, among them those of Denker (1913), Fraser (1922), Denker (1927), Albrecht (1940), Altmann (1950), Guli and Bonetti (1956), and Ormerod (1960).

In the case of recessive deafness, the correlation between pathological, clinical, and genetical findings is surprisingly good, considering the difficulties involved. Changes seem to be uniformly of the type first described clearly by Scheibe (1892) and involve degeneration of the organ of Corti, sometimes predominantly of the basal coil, and abnormalities of the stria vascularis, tne tectorial membrane, and the spiral ganglion. Evidence about more central auditory tract and brain degeneration is sparse, but probably the hearing pathway beyond the spiral ganglion is normal. The vestibular apparatus is affected to a variable extent but its involvement is very pronounced in cases with the syndrome of deafness with retinitis pigmentosa (Siebenmann and Bing, 1907). There are no abnormalities of structure of the bony labyrinth or the middle ear. No post-mortem examination of the ear of a well-documented case of the syndrome of deafness with goitre is available.

The syndrome of deafness with unique electrocardiographic disturbances (see page 127) is an exception to the rule that the deaf do not die of causes related to their deafness. Several affected children have died while under observation, and Fraser *et al.* (1964a) report the post-mortem examination of the temporal bones of one such girl. Changes of the type described by Scheibe (1892) are present; vestibular involvement is not marked. While histochemical studies of the labyrinths of deaf persons are rare, it may be of significance that lobules of periodic acid-Schiff-positive material were found in the stria vascularis that were similar to those found in the ears of a case of deafness with retinitis pigmentosa (slides prepared from the case of Nager, 1927) and of a case of clinically undifferentiated recessive deafness by Buch and Jørgensen (1963). Fraser *et al.* (1964a) have also examined the hearts of two children of their series and have found that the normal glycogen-containing perinuclear zone is absent in the Purkinje nerve fibres. While the relevance of this finding to the ECG abnormalities is not clear, it is of considerable interest in view of the fact that glycogen is normally present in considerable amounts in the hair cells of the normal organ of Corti of guinea-pigs and is thought to play an important role in their anaerobic metabolism (Falbe-Hansen and Thomsen, 1963).

These pathological findings correlate very well with the predominantly high-tone deafness, at any

rate in younger age-groups, associated with recessive deafness and the infrequent presence of disturbances of vestibular function except in the case of the syndrome of deafness with retinitis pigmentosa. They also correlate very well, allowing for differences in the methods of collection and preparation, with the findings in deaf mice (see page 121) and guinea-pigs (Lurie, 1941). Recessive deafness in these laboratory animals is also marked by an earlier degeneration of the basal part of the membranous cochlea and variable involvement of the vestibular apparatus. In most cases the structure of the bony labyrinth is normal, though mutants in mice are known in which recessive bony deformities do occur, either with deafness (Hertwig, 1944) or without (Truslove, 1956).

In the case of dominant deafness, on the other hand, the correlation of pathological with clinical and genetical findings is poor except in the case of Waardenburg's (1951) syndrome in which predominantly high-tone deafness is associated with histological changes similar to those found in recessive deafness (Fisch, 1959). Similar changes are found in dominant deafness associated with spotting of the coat colour in dogs (Lurie, 1948) and in 'varitint-waddler' mice (Deol, 1954), and in dominant deafness in white cats (Alexander, 1900; Wilson and Kane, 1959). The status of the malformation of the bony labyrinth first described by Mondini (1791) is unclear, as is the relation of the entity of 'progressive dominant heredo-labyrinthine deafness' with which it is supposed to be associated to dominant profound childhood deafness. The flatter and even saucer-shaped (Mårtensson, 1960; Williams and Roblee, 1962) patterns of hearing loss associated with these conditions may betoken a different pathogenesis from that involved in recessive deafness. Radiology could be of considerable assistance since malformations of the bony labyrinth can now be seen on special x-ray views. In uncomplicated sex-linked recessive deafness the audiogram is also relatively flat; no post-mortem examination of a well-documented case is available. Wolff (1942), however, has examined at necropsy the ears of a deaf male with sex-linked recessive gargoylism (see page 132) and has found changes of the Scheibe type affecting the membranous labyrinth.

If the status of the Mondini (1791) malformation is far from clear, that of Michel (1863) rests on even less sure foundations. Though clinical and genetical details are lacking, this isolated observation of the total absence of the inner ear and auditory nerves has been handed down and passed on through several hundred publications and considered to represent an important class of profound childhood deafness. This lesion may be related to that described by Everberg *et al.* (1963) on radiological evidence in deafness associated with the Klippel-Feil syndrome.

Deafness due to profound neonatal jaundice (see page 140) is thought to be due to the central toxic effect of bilirubin on the cochlear nuclei, especially those concerned with the transmission of high tones (Crabtree and Gerrard, 1950; Fisch, 1955b). The flat audiogram in deafness due to maternal rubella is considered to be due to the fact that it represents an interference with normal maturation processes rather than a postnatal degeneration of the organ of Corti; the end result is histologically much the same (Lindsay and Harrison, 1954). Finally Altmann (1949, 1955) has provided scholarly reviews of the pathological processes associated with congenital atresia of the ear in man and animals. As discussed above (see page 136), these are often associated with malformation of the middle ear but only rarely with changes in the inner ear.

VI: An Attempt at a Synthesis

The complexity of the problem of the causation of profound childhood deafness is amply illustrated by the heterogeneity revealed in these pages. Many surveys have taken place in recent years with as many proposed classifications and numerical assessments of the various causes involved. None of these surveys is free of defects; nor in view of the difficulties involved can perfection be expected.

Three types of investigative procedure have been followed. The first, of which the more notable examples have been mentioned on page 121, has been to ascertain completely all deaf persons within a limited geographical area, supported by extensive family studies. The second is to survey groups of children segregated in special schools, and this approach may sometimes overlap with the first, as in the series of Furusho (1957) from Japan. Other examples of this type are the studies of Henning (1928) in Sweden, Shambaugh *et al.* (1928, 1930), Hughson, Ciocco, and Palmer (1942), Hopkins and Guilder (1949) (with extensive genetical analysis of the pedigrees by Hopkins *et al.* (1946)) and Danish *et al.* (1963) from the U.S.A., Lamy *et al.* (1949) in France, Arnvig (1954) in Denmark, Wildervanck (1957a) in Holland, Bernabei and di Brino (1957) in Italy, and Barton *et al.* (1962) and Fraser (1962a, 1964a) in the British Isles.

The third type of investigation, which again overlaps to some extent with the second, has been the study of children referred to otological clinics, and such series have been reported in many parts of the world. They include those of Goodhill (1950), Bordley and Hardy (1951), Fowler and Basek (1954), and Zonderman (1959) from the U.S.A., Hata (1955) from Hawaii, Siedlanowska (1955) from Poland, Finzi and Leonardelli (1956) from Italy, Lacina and Sedláčková (1957) from Czechoslovakia, Liu, Liu, Li, Teng, and T'an (1957) from China, Suzuki *et al.* (1960) from Japan, Gerc (1960) from Yugoslavia, and Ballantyne (1960), Livingstone (1961) and Whetnall and Fry (1964) from England.

All these three types of survey have their advantages and their disadvantages and all cover a slightly different aspect of the problem. The different methods of selection involved and the different interests of the investigators will influence the spectrum of causes; all these surveys are isolated in space and time and further heterogeneity is introduced on this account. Yet all these and many more such investigations are needed to obtain a composite picture of the total biological burden of profound childhood deafness such as is discussed, from different viewpoints, by Wildervanck (1953), van Egmond (1954), Cawthorne and Hinchcliffe (1957), Cerri and Maffei (1958), Whetnall and Fry (1964), Schwarz, Becker, and Jørgensen (1964), and Froggatt (1964) among others.

It is difficult to obtain a reliable estimate of the prevalence of profound childhood deafness. If the definition of the introduction is extended to cover those who are ineducable and those who are able to follow normal schooling but with difficulty, such as are revealed by the surveys of Kinney (1953) in the U.S.A. and Johnsen (1954a, b) in Denmark, then certainly 1 per 1,000 of the child population would not anywhere be an overestimate, and in some parts of the world with a relatively low standard of medical care would be a gross underestimate.

Based on the considerations adumbrated in this review, this load of deafness may be tentatively apportioned by cause (Table). The figures expressed as percentages of the total are equivalent to actual numbers per 100,000 births in the general population. It must be remembered that this balance sheet refers to the present day in economically advanced societies with high standards of medical care and that, in some cases, it involves approximations and assumptions that form the basis of the analysis of the data of Fraser (1962a, 1964a, 1965b), the nature of which has only partly been explained in these pages.

TABLE

			Percentage
Genetical	Recessive	With retinitis pigmentosa	7·5
		With goitre	3·0
		With abnormal ECG	1·0
		Others	26·0
	Dominant	With pigmentary anomalies	2·5
		Without pigmentary anomalies	10·0
	Sex-linked		1·5
Acquired	Prenatally		6·0
	Perinatally (including excess of prematurity)		10·0
	Postnatally (after the end of the perinatal period)		30·0
Congenital malformations			2·5

It may be expected that the proportion of profound childhood deafness attributable to acquired causes will fall with improved medical care during pregnancy, birth, infancy, and childhood, especially as awareness of the particular dangers to which the auditory apparatus is exposed increases. The question of the treatment and prevention of hereditary deafness is, on the other hand, a long-term problem to which no easy solution is in sight. In the meantime, further study of the various components of hereditary deafness cannot fail to provide insight into the pathways of gene action involved which, in turn, will throw light on many presently obscure aspects of normal embryogenesis and normal postnatal physiology and biochemistry.

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Corrigenda

A Family Apparently Showing Transmission of a Translocation between Chromosome 3 and one of the 'X-6-12' or 'C' Group. G. Clarke, A. C. Stevenson, Pamela Davies, and C. E. Williams. Vol. **1**, p. 27.

The Table on p. 31 requires the following corrections:

II.5	Substitute MSMs for MNS	III.7	Substitute MSNs for MsNs
II.6	,, MSMs for MMs	III.7	,, R_1r for R_2r