Recent advances in ophthalmic genetics

Genetic counselling

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Contributed by request and dedicated to Sir Stewart Duke-Elder

Considerable advances have been made in our knowledge of human genetics since Sir Stewart wrote the section on "Heredity" in his "System of Ophthalmology" (Duke-Elder, 1962) just over 10 years ago. Many of these advances have influenced our management of patients with genetically-determined disorders and, in particular, have improved our accuracy in calculating the risks of recurrence of hereditary diseases. With the increasing knowledge of genetics among the general population, and with their increasing desire to plan their families, the demand for genetic counselling has grown considerably in recent years. Genetic counselling is concerned both with making an accurate assessment of the genetic risk and with explaining this risk to those seeking advice. Accurate assessment of genetic risk depends firstly on an accurate diagnosis, secondly on a good family history with verification of relevant medical information from hospital or other records, and thirdly on knowledge of the way in which the particular condition is inherited (Carter, 1969). It is the purpose of this paper to discuss some of the advances that have taken place in the past decade which have influenced our assessment of genetic risk in hereditary disorders of the eye.

Genetic heterogeneity

"Genetic heterogeneity (two or more fundamentally distinct entities that share approximately the same phenotype) is the rule. If a disorder is thought to be a single entity, it usually means that the disorder is not well understood." McKusick (1972)

The importance of an accurate diagnosis in assessing genetic risk cannot be overemphasized, particularly when the family history does not give a clear indication of the mode of transmission. It has become apparent that in many instances more than one genetic cause leads to the same or a similar clinical appearance (heterogeneity), and what was once thought to be a single entity has proved on close study to consist of several distinct disorders. Three examples of genetic heterogeneity will be used to illustrate this point.

Albinism

One of the original "Inborn Errors of Metabolism" described by Sir Archibald Garrod (1909) was albinism, a condition of considerable antiquity widely distributed both in the various races of man and in the rest of the animal kingdom. Albinism has for long been of interest to ophthalmologists and one of the earliest classifications of this heterogeneous group of disorders was that of Pearson, Nettleship, and Usher (1911-13). Their classification,

although inaccurate and incomplete in the light of our present knowledge, was not superseded until Fitzpatrick and Quevedo (1966), divided albinism into oculocutaneous, ocular, and cutaneous forms. More recently, Witkop (1971) has further subdivided oculocutaneous albinism on the basis of the tyrosinase test (Kugelman and Van Scott, 1961) into tyrosinase-positive and tyrosinase-negative forms. His study of two families (Witkop, Nance, Rawls, and White, 1970), one being the family originally reported by Trevor-Roper (1952), demonstrated that parents with the two different forms of oculocutaneous albinism produce normal offspring, thus indicating that the genes responsible for these two forms are situated at different genetic loci. Witkop's classification of albinism (Witkop, 1971) includes a number of hypopigmentary disorders which Fitzpatrick and Quevedo (1972) believe should not now be included under the general heading of albinism; it is clinically useful, however, to consider these conditions together (Table I). It is Witkop's impression

Table I *Classification of albinism**

<i>Disorder</i>	<i>Indication</i>
Oculocutaneous	Tyrosinase test negative <ol style="list-style-type: none"> 1 Tyrosinase-negative oculocutaneous albinism 2 Albinism-haemorrhagic diathesis (Hermansky-Pudlak syndrome) Tyrosinase test positive <ol style="list-style-type: none"> 1 Tyrosinase-positive oculocutaneous albinism 2 Chediak-Higashi syndrome 3 Hypopigmentation-microphthalmus oligophrenia syndrome (Cross syndrome) Tyrosinase test variable <ol style="list-style-type: none"> 1 Yellow mutant
Ocular	<ol style="list-style-type: none"> 1 Ocular albinism 2 Forsius-Eriksson type (?)
Cutaneous	Without deafness <ol style="list-style-type: none"> 1 Piebaldism with white forelock 2 Questionable isolated white forelock 3 Questionable isolated occipital lock 4 Menkes' syndrome 5 Miscellaneous With deafness <ol style="list-style-type: none"> 1 Waardenburg syndrome 2 Ziprkowski-Margolis syndrome 3 Questionable cutaneous albinism with deafness

* Witkop (1971)

that visual acuity is better and that nystagmus and photophobia are less marked in the tyrosinase-positive than in the tyrosinase-negative form of oculocutaneous albinism (Witkop, 1971); this impression needs to be confirmed. Witkop, Niswander, Bergsma, Workman, and White (1972) also found that in tyrosinase-positive albinism the severity of nystagmus and photophobia decreased with age. It is possible, therefore, that the visual prognosis of children with oculocutaneous albinism might be determined by the result of the tyrosinase test; children who are tyrosinase-negative appear to be at greater risk of being severely

visually handicapped, while those who are tyrosinase-positive may develop a level of vision sufficient for normal schooling. It also appears desirable to attempt to exclude the Hermansky-Pudlak and Chediak-Higashi syndromes in all children with albinism, the former by the history of a bleeding diathesis, abnormal reticulo-endothelial cells, and possibly abnormal platelets, the latter by the presence of giant peroxidase-positive lysosomal granules in leucocytes.

Retinitis pigmentosa

A classical example of genetic heterogeneity is the group of disorders known as retinitis pigmentosa. For many years it has been recognized that isolated retinitis pigmentosa can be transmitted as an autosomal dominant, an autosomal recessive, or an X-linked trait, the last being considered by far the rarest (François, 1961; Ammann, Klein, and Franceschetti, 1965). Because of the wide range of expression in heterozygous (carrier) females, the X-linked form has in the past been subdivided into recessive, intermediate, and dominant types, although this subdivision has recently been questioned (Berson, Gouras, Gunkel, and Myrianthopoulos, 1969; Jay and Bird, 1973). In a recent study of retinitis pigmentosa in London, nearly one-quarter of the 106 families were found to have the X-linked form of the disease (Table II), a finding at variance with previous reports. It has also been shown that the different genetic forms of the disease have different visual prognoses; the majority

Table II *Incidence of different genetic forms of retinitis pigmentosa (per cent.)*

<i>Mode of transmission</i>	<i>François⁽¹⁾</i>	<i>Switzerland⁽²⁾</i>	<i>London⁽³⁾</i>
Autosomal recessive	37.0	90	17.0
Autosomal dominant	19.5	9	38.7
X-linked	4.5	1	23.6
Sporadic or uncertain	39.0	—	20.7

⁽¹⁾ François (1961) ⁽²⁾ Ammann and others (1965) ⁽³⁾ Jay and Bird (unpublished)

of affected individuals with the autosomal dominant form have a central vision of 6/18 or better at 50 years of age, while those with the autosomal recessive and X-linked forms usually have a central vision of 6/60 or less at 30 years of age (Jay, 1972). These observations are relevant, not only to genetic counselling, but also to studies aimed at determining the aetiology of retinitis pigmentosa. It is probable that each genetic form of the disease has a different underlying abnormality, and only by studying these different forms separately will meaningful conclusions be reached.

Mucopolysaccharidoses

While the underlying defects in the various genetic forms of isolated retinitis pigmentosa have not yet been established, considerable progress has recently been made in our understanding of another group of disorders which also demonstrates genetic heterogeneity, the mucopolysaccharidoses (Table III). These uncommon and rare disorders are of interest to ophthalmologists as several of the conditions in this group are associated with corneal clouding. All but MPS II, the Hunter syndrome which is X-linked, are transmitted as autosomal recessive traits.

Table III *Classification of mucopolysaccharidoses**

<i>Designation</i>		<i>Substance deficient</i>
MPS I H	Hurler syndrome	α -L-iduronidase
S	Scheie syndrome	α -L-iduronidase
H/S	Hurler-Scheie compound	α -L-iduronidase
MPS II A	Hunter syndrome, severe	Hunter corrective factor
B	Hunter syndrome, mild	Hunter corrective factor
MPS III A	Sanfilippo syndrome A	Heparan sulphate sulphatase
B	Sanfilippo syndrome B	N-acetyl- α -D-glucosaminidase
MPS IV	Morquio syndrome	Unknown
MPS V	—	—
MPS VI A	Maroteaux-Lamy syndrome classic form	Maroteaux-Lamy corrective factor
B	Maroteaux-Lamy syndrome mild form	Maroteaux-Lamy corrective factor
MPS VII	β -glucuronidase deficiency	β -glucuronidase

* McKusick (1972)

MPS I

The prototype mucopolysaccharidosis, MPS I H (Hurler syndrome), is characterized by dwarfing and mental retardation, a large head and characteristic facies, hepatosplenomegaly, and corneal clouding. Death usually occurs at about the age of 10 years. Excessive urinary excretion of dermatan sulphate and heparan sulphate occur, and a deficiency of the enzyme α -L-iduronidase has been demonstrated (Bach, Friedman, Weissmann, and Neufeld, 1972).

A milder condition, the Scheie syndrome (Scheie, Hambrick, and Barness, 1962), characterized by corneal clouding, deformities of the hands, and aortic valve disease, but with normal intelligence, has now been reclassified as MPS I S, since the basic defect is the same as in MPS I H, a deficiency of α -L-iduronidase (Bach and others, 1972).

It is probable that the genes for MPS I H and MPS I S are allelic (occurring at the same locus on a chromosome), and support for this is in the cases reported by McKusick, Howell, Hussels, Neufeld, and Stevenson (1972) which appear to be Hurler-Scheie compounds.

MPS II

The first detailed clinical description of a mucopolysaccharidosis was that by Hunter (1917) of two brothers who were dwarfed with gargoyle-like facies, claw hands, and hepatosplenomegaly, but with normal intelligence and clear corneae. They are now believed to have suffered from the X-linked MPS II. Mental deterioration develops as the affected males grow older and a mild corneal clouding occurs (Goldberg and Duke, 1967; Topping, Kenyon, Goldberg, and Maumenee, 1971). A pigmentary retinopathy develops in this condition, as it also does in MPS I H, MPS I S, and MPS III. Severe and mild forms of

MPS II can be distinguished clinically; both are associated with excessive urinary excretion of dermatan sulphate and heparan sulphate, and both show a deficiency of the same corrective factor (indicating that they are allelic forms), the nature of which has not yet been established.

MPS III

This type of mucopolysaccharidosis is characterized by severe mental retardation and relatively less severe somatic changes (Sanfilippo, Podosin, Langer, and Good, 1963). Clouding of the corneae does not occur although an acid mucopolysaccharide accumulates in the cornea (Jensen, 1971). Two clinically indistinguishable biochemical forms have been demonstrated, both associated with the urinary excretion of large amounts of heparan sulphate. One form is due to a deficiency of the enzyme heparan sulphate sulphatase, the other to a deficiency of N-acetyl- α -D-glucosaminidase.

MPS IV

The Morquio syndrome is characterized by extreme dwarfism, characteristic skeletal changes, gargoylike facies, and progressive corneal clouding, but normal intelligence. Most cases are associated with excessive urinary excretion of keratan sulphate; a few are not, and these are considered by McKusick (1972) to have a distinct form of MPS IV. Metachromatic granules are found in fibroblasts (Fraccaro, Mannini, Lenzi, Magrini, Perona, and Sartori, 1967; Danes and Bearn, 1967), but the fundamental defect has not yet been established.

MPS VI

The Maroteaux Lamy syndrome (Maroteaux, Lévêque, Marie, and Lamy, 1963), has many clinical features similar to those of MPS I H, although intellectual development is normal. Early corneal clouding is characteristic, the result of the accumulation of abnormal mucopolysaccharides both intracellularly and extracellularly (Kenyon, Topping, Green, and Maumenee, 1972). There is excessive urinary excretion of dermatan sulphate and the fundamental defect is the absence of a specific corrective factor. There is some evidence that MPS VI itself exhibits genetic heterogeneity, there being a clinically milder form also showing absence of the same specific corrective factor.

MPS VII

The most recent entity to be recognized as a specific mucopolysaccharidosis is MPS VII, β -glucuronidase deficiency (Beaudet, Di Ferrante, Nichols, and Ferry, 1972; Sly, Quinton, McAlister, and Rimoin, 1973). Clinical features include dwarfism, hepatosplenomegaly, and inclusions in leucocytes. So far, corneal changes have not been seen. McKusick (1972) gives a detailed account of this and other mucopolysaccharidoses.

Detection of heterozygous states

As our investigation of the heterozygous state becomes more sophisticated, so does its detection become more frequent. In X-linked traits where the abnormality is manifested in (hemizygous) males, and occasionally in homozygous females, it is becoming increasingly common for minor abnormalities to be described in heterozygous ("carrier") females. The identification of these heterozygous females is particularly important in genetic

counselling, as 50 per cent. of their male offspring will be affected. The advent of amniocentesis, which allows the determination of fetal sex early in pregnancy, offers the opportunity for a therapeutic abortion of a male fetus if the condition is severe.

In "Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes" (McKusick, 1971), about 30 per cent. of those conditions considered to be definitely X-linked are ophthalmological, or have major ophthalmological components. In about half of these, abnormalities have been reported in heterozygous females (Table IV). These abnormalities vary considerably in severity

Table IV *Detection of heterozygous states in X-linked traits with ophthalmic manifestations*

<i>McKusick catalogue</i>	<i>Disorder</i>	<i>Appearance of heterozygous state</i>	<i>Reference</i>
30050	Albinism, ocular	Characteristic fundus appearance in some heterozygotes	Vogt (1942) Falls (1951)
30060	Albinism, ocular (Forsius-Eriksson type)	Normal	Forsius and Eriksson (1964)
30070	Albinism-deafness syndrome	Impaired hearing	Fried, Feinmesser, and Tsitsianov (1969)
30150	Angiokeratoma, diffuse (Fabry's disease)	Whorl-like corneal dystrophy	Rahman (1963) Franceschetti, Philippart, and Franceschetti (1969)
30220	Cataract, congenital total	Posterior sutural opacities	Krill, Woodbury, and Bowman (1969)
30310	Choroideremia	Characteristic fundus appearance	McCulloch and McCulloch (1948) Kurstjens (1965)
30370	Colour blindness, blue-monocone monochromatic type	Normal	Spivey (1965)
30380	Colour blindness, partial, deutan series	Very slight defects of colour vision	Waardenburg (1963) Kalmus (1965)
30390	Colour blindness, partial, protan series		
30400	Colour blindness, partial, tritanomaly		
30510	Ectodermal dysplasia, anhidrotic		
30540	Faciogenital dysplasia	Defects of teeth, sweat glands, heart	Kerr, Wells, and Cooper (1966)
30880	Keratos follicularis spinulosa decalvans cum ophiasis	? Short stature Corneal erosions	Aarskog (1970) Forgacs and Franceschetti (1959)
30900	Lowe's oculocerebrorenal syndrome	Lens opacities	Richards, Donnell, Wilson, Stowens, and Perry (1965)
30930	Megalocornea	Slight increase in corneal diameter	Riddell (1941)
30980	Microphthalmia or anophthalmia with digital anomalies	Digital anomalies	Lenz (1955)
30990	Mucopolysaccharidosis II	Metachromatic cytoplasmic inclusions in fibroblasts	Danes and Bearn (1967)
31050	Night blindness, congenital stationary, with myopia	Normal	Duke-Elder (1964)
31060	Norrie's disease	Normal	Warburg (1971)
31100	Ophthalmoplegia, external, and myopia	Absent deep reflexes	Ortiz de Zarate (1966)
31160	Pelizaeus-Merzbacher disease	Normal	Rahn, Yanoff, and Tucker (1968)
31260	Retinitis pigmentosa	Characteristic fundus appearance	Falls and Cotterman (1948) Jay and Bird (1973)
31270	Retinoschisis	Normal	Kraushar, Schepens, Kaplan, and Freeman (1972)
31450	Van den Bosch syndrome	Normal	Van den Bosch (1959)

from one disorder to another, and even in one disorder from one heterozygote to another. In some disorders the heterozygous state can easily be ascertained clinically, in some the abnormalities are inconstantly present, while in others the heterozygous phenotype varies from almost normal to a severity almost equal to that of affected males. Examples of this variability of the heterozygous state will be given.

Choroideremia

The appearance of the fundus in females heterozygous for choroideremia was first described as such by Waardenburg (1942) and Goedbloed (1942), although there are earlier reports in the literature of mild fundus changes in female relatives of patients with choroideremia without the significance of these changes having been appreciated. In most of these earlier reports the changes were described as pigment anomalies, most marked in the

periphery of the retina, and were considered to be congenital and stationary and not usually associated with any functional deficit. Kurstjens (1965) described his findings in 45 affected males and 61 heterozygous females. In the females the striking feature was the wide variation in the appearance of the fundus, ranging from very slight pigmentary changes in the retina to features closely resembling those seen in affected males; there was also considerable intrafamilial variation in these changes. In four of these heterozygous females progression of the changes in the fundus were noted, associated with a reduction in the visual acuity. Three of these four heterozygotes complained of night-blindness, had abnormal dark adaptation curves, extensive defects in their visual fields, severe electroretinographic changes, and an absence of light rise in the electro-oculogram. These progressive changes in the fundus, associated with functional deficits, were observed to occur later in life than in affected males. In this large group of heterozygous females, the most common appearance of the fundus was, however, the presence of fine equatorial and peripheral pigmentation, often in a striated and radiating pattern, and unassociated with functional deficits.

Retinitis pigmentosa

The appearance of the fundus in females heterozygous for X-linked retinitis pigmentosa has been of particular interest since the description of the tapetal reflex by Falls and Cotterman (1948). A number of isolated reports have appeared over the past 25 years, but it is the two large studies by Schappert-Kimmijser (1963) and by Jay and Bird (1973) that have indicated the wide interfamilial and intrafamilial variation in the appearances of the fundus in these heterozygous females. In the series of nineteen families reported by Jay and Bird (1973), 42 heterozygous females were examined, 39 of whom had a visual acuity better than 6/18. Several females who were presumed to have been heterozygous but who were not examined were said to have become blind in old age. Almost all heterozygous females had changes in the fundus. A few had a glistening tapetal reflex, but this was neither a common nor a particularly helpful change. A number had a characteristic granular retinal periphery with small white dots scattered over it. The most characteristic changes were segmental areas of atrophy of the pigment epithelium with pigmentary migration into the retina. A few fundi showed segmental retinitis pigmentosa or even frank generalized retinitis pigmentosa. Small defects in the visual fields were usually demonstrable corresponding to the areas of greatest retinal involvement. In those heterozygous females with gross retinal changes, the field changes were correspondingly gross, but never as extensive as the changes found in affected males of similar age. The final rod threshold of dark adaptation was almost always raised by 0.5 to 1.5 log units in patients with minor involvement, the EOG light-induced rise in potential was usually between 100 and 160 per cent., and ERG changes occurred in the more severely affected females.

Identification of carriers

The importance of identifying heterozygous females in X-linked conditions is obvious, as 50 per cent. of their male offspring will be affected. The identification of heterozygotes (carriers) in autosomal recessive conditions is far less often of practical importance. Autosomal recessive conditions tend to be uncommon or rare and the chances of a carrier marrying another carrier with the same abnormal gene are very small, as long as they are not related. In certain instances, however, this identification of the carrier state is relevant, particularly in the screening of whole populations especially at risk. Such identification is already being carried out in parts of Italy, where 10 per cent. or more of the population

carry the gene for thalassaemia; it has been suggested for the sickle-cell trait in Negroes, so that couples found to be at risk can be offered antenatal diagnosis to prevent the birth of affected children (Hollenberg, Kaback, and Kazazian, 1971); and it is being carried out in parts of North America among Ashkenazi Jews who are at particular risk of carrying the gene for Tay-Sachs disease (Delvin, Scriver, Pottier, Clow, and Goldmann, 1972). In this last disease, Aronson and Volk (1962) have estimated the carrier rate to be nearly 1:30 in the Jewish population of New York City, compared with an estimated carrier rate of about 1:300 in non-Jewish Americans. A screening programme to test for heterozygosity to Tay-Sachs disease has recently been established in London (Evans, 1973). The identification of the carrier state in autosomal recessive disorders is still in its infancy. It is inevitable that, with the demonstration of the basic enzymatic defect in each of these conditions, and with the increasingly sophisticated biochemical estimations of these enzymes, the list of disorders in which the carrier state will be identifiable will grow very fast over the next few years.

Antenatal diagnosis

About 20 years ago it was shown that the sex of a fetus could be determined by examining the sex chromatin of cells in amniotic fluid. About 10 years ago these cells were cultured and their chromosomes studied, thus determining the chromosome constitution of the fetus. Nadler (1968) demonstrated that these fetal cell cultures could be used for the antenatal diagnosis of certain biochemical disorders. In ophthalmic genetic counselling we are particularly concerned with the determination of fetal sex and with the identification of certain genetically-determined disorders by studying amniotic fluid, a study which can now be undertaken at about 14 weeks of pregnancy. No mention will be made here of chromosome studies, a subject which does not fall within the scope of this article.

The determination of fetal sex is relevant in conditions transmitted by genes on the X-chromosome. An affected male with an X-linked disorder will produce normal sons and heterozygous (carrier) daughters, while a female who is heterozygous for an X-linked disorder will produce 50 per cent. affected sons and 50 per cent. carrier daughters. In X-linked disorders with severe effects, it is reasonable to consider the termination of a pregnancy if there is a 'substantial risk' of a serious abnormality in the fetus. The determination of fetal sex by amniocentesis can therefore be offered to heterozygous females as long as termination of the pregnancy would be acceptable if the fetus were male. Amniocentesis can be offered, for example, to those heterozygous females for X-linked retinitis pigmentosa or for choroideremia who do not wish to produce an affected son. The long-term dysgenic effects of this policy have to be considered. The abortion of all males from carrier mothers with full reproductive compensation (the ultimate size of the family being unaffected by any terminations of pregnancy that are performed) will result in the gene frequency rising linearly with time (Motulsky, Fraser, and Felsenstein, 1971). However, this rise will probably be slow and its dysgenic effect on the gene pool less important than other factors which influence gene frequency.

The detection of biochemical abnormalities in the fetus by demonstrating the absence of a specific enzyme or the presence of an abnormal metabolite in amniotic fluid cells is still in its infancy, so much so that only two conditions, Tay-Sachs disease and Pompe's disease, have been diagnosed in any number. As a rule, this detection is required in a second pregnancy after the birth of an affected infant in conditions transmitted as autosomal recessive traits. When one such affected infant has been produced, the chances of further offspring being affected are 25 per cent. The number of disorders which have been diag-

nosed antenatally, or in which a method for diagnosis has been described, is growing rapidly; those conditions with ophthalmic manifestations at present capable of being diagnosed are given in Table V.

Table V Disorders with ophthalmic manifestations diagnosed in utero, or in which a* method for diagnosis has been described using cultured amniotic fluid cells

Disorder	Deficient enzyme or other feature in cell culture	Reference
Diffuse angiokeratoma (Fabry's disease)	α -galactosidase	Brady, Uhlendorf, and Jacobson (1971)
Cystinosis (Fanconi syndrome)	Increased incorporation of ^{35}S -cystine	Schulman, Fujimoto, Bradley, and Seegmiller (1970)
Galactokinase deficiency	Galactokinase	Benson, Blunt, and Brown (1973)
Galactosaemia	Galactose-1-phosphate uridyl transferase	Nadler (1968)
GM ₁ gangliosidosis, type 1 (generalized gangliosidosis)	β -galactosidase	Kaback, Sloan, Sonneborn, Herndon, and Percy (1973)
GM ₂ gangliosidosis, type 1 (Tay-Sachs disease)	Hexosaminidase A	O'Brien, Okada, Fillerup, Veath, Adornato, Brenner, and Leroy (1971)
GM ₂ gangliosidosis, type 2 (Sandhoff's disease)	Hexosaminidase A and B	Okada, McCrea, and O'Brien (1972)
Homocystinuria	Cystathionine synthase	Bittles and Carson (1973)
Globoid cell leucodystrophy (Krabbe's disease)	Galactocerebroside β -galactosidase	Suzuki, Schneider, and Epstein (1971)
Metachromatic leucodystrophy	Arylsulphatase A (see text)	Nadler and Gerbie (1970)
Mucopolysaccharidoses	Sphingomyelinase	Epstein, Brady, Schneider, Bradley, and Shapiro (1971)
Niemann-Pick disease		Uhlendorf, Jacobson, Sloan, Mudd, Herndon, Brady, Seegmiller, and Fujimoto (1969)
Refsum's syndrome	Phytanate α -hydroxylase	

(* Modified from Harvey, 1973)

Antenatal diagnosis is most likely to be successful when the basic enzymatic defect is known and when the enzyme has wide tissue distribution. If the enzyme is expressed in cultured skin fibroblasts, it will probably be demonstrable in amniotic fluid cells. It is only recently that the basic enzymatic defects have been demonstrated for some of the mucopolysaccharidoses (Table III) and as yet there are no reports in the literature of antenatal diagnosis being based on their absence from amniotic fluid cells. Up to the present time, the antenatal diagnosis of the mucopolysaccharidoses has depended upon the increased incorporation of radioactive sulphate in cultured amniotic fluid cells (Fratantoni, Neufeld, Uhlendorf, and Jacobson, 1969), or upon the analysis of mucopolysaccharides in amniotic fluid (Matalon, Dorfman, Nadler, and Jacobson, 1970). The problems inherent in these methods are discussed by Crawford, Dean, Hunt, Johnson, MacDonald, Muir, Wright, and Wright (1973). It is expected that a direct assay of the specific enzyme in amniotic cells will soon be possible in this group of disorders, as it will in many other inborn errors of metabolism. For a detailed account of the current position in the antenatal diagnosis of genetic disease, reference should be made to Emery (1973).

Summary

Some of the recent advances which have influenced our assessment of genetic risk in hereditary disorders of the eye are discussed. The importance of making an exact diagnosis is emphasized, and the concept of genetic heterogeneity is illustrated by three groups of disorders: albinism, retinitis pigmentosa, and the mucopolysaccharidoses. The value of recognizing the heterozygous state in X-linked and in autosomal recessive traits is discussed and the clinical variability of heterozygotes for choroideremia and for X-linked retinitis pigmentosa is described. Two aspects of antenatal diagnosis are considered. The implications of the determination of foetal sex for females heterozygous for X-linked traits is discussed. The current position regarding the detection of biochemical abnormalities in the foetus is stated.

References

- AARSKOG, D. (1970) *J. Pediat.*, **77**, 856
- AMMANN, F., KLEIN, D., and FRANCESCHETTI, A. (1965) *J. neurol. Sci.*, **2**, 183
- ARONSON, S. M., and VOLK, B. W. (1962) "Genetic and demographic considerations concerning Tay-Sachs disease" in "Cerebral Sphingolipidoses", ed. S. M. Aronson and B. W. Volk, p. 375. Academic Press, New York
- BACH, G., FRIEDMAN, R., WEISSMANN, B., and NEUFELD, E. F. (1972) *Proc. nat. Acad. Sci. (Wash.)*, **69**, 2048
- BEAUDET, A. L., DIFERRANTE, N., NICHOLS, B., and FERRY, G. D. (1972) *Amer. J. hum. Genet.*, **24**, 25a
- BENSON, P. F., BLUNT, S., and BROWN, S. P. (1973) *Lancet*, **1**, 106
- BERSON, E. L., GOURAS, P., GUNKEL, R. D., and MYRIANTHOPOULOS, N. C. (1969) *Arch. Ophthal. (Chicago)*, **81**, 215
- BITTLES, A. H., and CARSON, N. A. J. (1973) *J. med. Genet.*, **10**, 120
- BOSCH, J. VAN DEN (1959) *Ophthalmologica (Basel)*, **137**, 422
- BRADY, R. O., UHLENDORF, B. W., and JACOBSON, C. B. (1971) *Science (N.Y.)*, **172**, 174
- CARTER, C. O. (1969) "An ABC of Medical Genetics", p. 62. *Lancet*, London
- CRAWFURD, M. D'A., DEAN, M. F., HUNT, D. M., JOHNSON, D. R., MACDONALD, R. R., MUIR, H., PAYLING WRIGHT, E. A., and PAYLING WRIGHT, C. R. (1973) *J. med. Genet.*, **10**, 144
- DANES, B. S., and BEARN, A. G. (1967) *J. exp. Med.*, **126**, 509
- DELVIN, E. E., SCRIVER, C. R., POTTIER, A., CLOW, C. L., and GOLDMANN, H. (1972) *Un. méd. Can.*, **101**, 683
- DUKE-ELDER, S. (1962) "A System of Ophthalmology", vol. 7, pp. 3-113. Kimpton, London
- (1964) *Idem*, vol. 3, pt 2, p. 660
- EMERY, A. E. H. (1973) "Antenatal Diagnosis of Genetic Disease". Churchill, Livingstone, Edinburgh
- EPSTEIN, C. J., BRADY, R. O., SCHNEIDER, E. L., BRADLEY, R. M., and SHAPIRO, D. (1971) *Amer. J. hum. Genet.*, **23**, 533
- EVANS, P. R. (1973) *Brit. med. J.*, **3**, 408
- FALLS, H. F. (1951) *Amer. J. Ophthal.*, **34**, 41
- and COTTERMAN, C. W. (1948) *Arch. Ophthal. (Chicago)*, **40**, 685
- FITZPATRICK, T. B., and QUEVEDO, W. C. (1966) "Albinism", in "The Metabolic Basis of Inherited Disease", 2nd ed., ed. J. B. Stanbury, J. B. Wyngaarden, and D. S. Fredrickson, p. 324. McGraw-Hill, New York
- (1972) *Idem*, 3rd ed., p. 326
- FORGACS, J., and FRANCESCHETTI, A. (1959) *Amer. J. Ophthal.*, **47**, Suppl., p. 191
- FORSIUS, H., and ERIKSSON, A. W. (1964) *Klin. Mbl. Augenheilk.*, **144**, 447
- FRACCARO, M., MANNINI, A., LENZI, L., MAGRINI, U., PERONA, P., and SARTORI, E. (1967) *Lancet*, **1**, 508
- FRANCESCHETTI, A. T., PHILIPPART, M., and FRANCESCHETTI, A. (1969) *Dermatologica (Basel)*, **138**, 209
- FRANÇOIS, J. (1961) *Proc. roy. Soc. Med.*, **54**, 1109
- FRATANTONI, J. C., NEUFELD, E. F., UHLENDORF, B. W., and JACOBSON, C. B. (1969) *New Engl. J. Med.*, **280**, 686
- FRIED, K., FEINMESSER, M., and TSITSIANOV, J. (1969) *J. med. Genet.*, **6**, 132
- GARROD, A. (1909) "Inborn Errors of Metabolism". Frowde, London
- GOEDBLOED, J. (1942) *Ophthalmologica (Basel)*, **104**, 308
- GOLDBERG, M. F., and DUKE, J. R. (1967) *Arch. Ophthal. (Chicago)*, **77**, 503
- HARVEY, D. (1973) *Brit. J. Hosp. Med.*, **10**, 591
- HOLLENBERG, M. D., KABACK, M. M., and KAZAZIAN, H. H. (1971) *Science (N.Y.)*, **174**, 698
- HUNTER, C. (1917) *Proc. roy. Soc. Med.*, **10**, 104
- JAY, B. (1972) *Trans. ophthal. Soc. U.K.*, **92**, 173
- and BIRD, A. (1973) *Trans. Amer. Acad. Ophthal. Otolaryng.*, **77**, 641
- JENSEN, O. A. (1971) *Acta path. microbiol. scand.*, **79A**, 257
- KABACK, M. M., SLOAN, H. R., SONNEBORN, M., HERNDON, R. M., and PERCY, A. K. (1973) *J. Pediat.*, **82**, 1037
- KALMUS, H. (1965) "Diagnosis and Genetics of Defective Colour Vision". Pergamon Press, Oxford
- KENYON, K. R., TOPPING, T. M., GREEN, W. R., and MAUMENEE, A. E. (1972) *Amer. J. Ophthal.*, **73**, 718
- KERR, C. B., WELLS, R. S., and COOPER, K. E. (1966) *J. med. Genet.*, **3**, 169

- KRAUSHAR, M. F., SCHEPENS, C. L., KAPLAN, J. A., and MACKENZIE FREEMAN, H. (1972) "Congenital Retinoschisis", in "Contemporary Ophthalmology honoring Sir Stewart Duke-Elder", ed. J. G. Bellows, p. 265. Williams and Wilkins, Baltimore
- KRILL, A. E., WOODBURY, G., and BOWMAN, J. E. (1969) *Amer. J. Ophthalm.*, **68**, 867
- KUGELMAN, T. P., and VAN SCOTT, E. J. (1961) *J. invest. Derm.*, **37**, 73
- KURSTJENS, J. H. (1965) *Docum. Ophthalm.*, **19**, 1
- LENZ, W. (1955) *Z. Kinderheilk.*, **77**, 384
- MCCULLOCH, C., and MCCULLOCH, R. (1948) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **52**, 160
- MCKUSICK, V. A. (1971) "Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes", 3rd ed. Johns Hopkins, Baltimore
- (1972) "Heritable Disorders of Connective Tissue", 4th ed., pp. 30, 521. Mosby, St Louis
- , HOWELL, R. R., HUSSELS, I. E., NEUFELD, E. F., and STEVENSON, R. (1972) *Lancet*, **1**, 993
- MAROTEAUX, P., LÉVÊQUE, B., MARIE, J., and LAMY, M. (1963) *Presse méd.*, **71**, 1849
- MATALON, R., DORFMAN, A., NADLER, H. L., and JACOBSON, C. B. (1970) *Lancet*, **1**, 83
- MOTULSKY, A. G., FRASER, G. R., and FELSENSTEIN, J. (1971) *Birth Defects*, **7**, 22
- NADLER, H. L. (1968) *Pediatrics*, **42**, 912
- and GERBIE, A. B. (1970) *New Engl. J. Med.*, **282**, 596
- O'BRIEN, J. S., OKADA, S., FILLERUP, D. L., VEATH, M. L., ADORNATO, B., BRENNER, P. H., and LEROY, J. G. (1971) *Science (N.Y.)*, **172**, 61
- OKADA, S., MCCREA, M., and O'BRIEN, J. S. (1972) *Pediat. Res.*, **6**, 606
- ORTIZ DE ZARATE, J. C. (1966) *Brit. J. Ophthalm.*, **50**, 606
- PEARSON, K., NETTLESHIP, E., and USHER, C. H. (1911-13) "A Monograph on Albinism in Man". Drapers' Company, London
- RAHMAN, A. N. (1963) *Arch. Ophthalm. (Chicago)*, **69**, 708
- RAHN, E. K., YANOFF, M., and TUCKER, S. (1968) *Amer. J. Ophthalm.*, **66**, 1143
- RICHARDS, W., DONNELL, G. N., WILSON, W. A., STOWENS, D., and PERRY, T. (1965) *Amer. J. Dis. Child.*, **109**, 185
- RIDDELL, W. J. (1941) *Ann. Eugen.*, **11**, 102
- SANFILIPPO, S. J., Podosin, R., LANGER, L., and GOOD, R. A. (1963) *J. Pediat.*, **63**, 837
- SCHAPPERT-KIMMISER, J. (1963) *Bull. Soc. franç. Ophthalm.*, **66**, 122
- SCHEIE, H. G., HAMBRICK, G. W., and BARNES, L. A. (1962) *Amer. J. Ophthalm.*, **53**, 753
- SCHULMAN, J. D., FUJIMOTO, W. Y., BRADLEY, K. H., and SEEGLER, J. E. (1970) *J. Pediat.*, **77**, 468
- SLY, W. S., QUINTON, B. A., MCALISTER, W. H., and RIMOIN, D. L. (1973) *Ibid.*, **82**, 249
- SPIVEY, B. E. (1965) *Arch. Ophthalm. (Chicago)*, **74**, 327
- SUZUKI, K., SCHNEIDER, E. L., and EPSTEIN, C. J. (1971) *Biochem. biophys. Res. Comm.*, **45**, 1363
- TOPPING, T. M., KENYON, K. R., GOLDBERG, M. F., and MAUMENEE, A. E. (1971) *Arch. Ophthalm. (Chicago)*, **86**, 164
- TREVOR-ROPER, P. D. (1952) *Brit. J. Ophthalm.*, **36**, 107
- UHLENDORF, B. W., JACOBSON, C. B., SLOAN, H. R., MUDD, S. H., HERNDON, J. H., BRADY, R. O., SEEGLER, J. E., and FUJIMOTO, W. (1969) In "Hemic Cells *in vitro*: a Symposium", ed. P. Farnes, Puerto Rico, 1968, p. 158. Williams and Wilkins, Baltimore (*In Vitro*, vol. 4)
- VOGT, A. (1942) "Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges", vol. 3, p. 846. Enke, Stuttgart
- WAARDENBURG, P. J. (1942) *Acta ophthalm. (Kbh.)*, **20**, 235
- (1963) "Genetics and Ophthalmology", vol. 2, pp. 1425-1567. Van Gorcum, Assen
- WARBURG, M. (1971) "Norrie's Disease", in "Birth Defects: Original Article Series", ed. D. Bergsma, vol. 7, no. 3, p. 117. Williams and Wilkins, Baltimore
- WITKOP, C. J. (1971) "Albinism", in "Advances in Human Genetics", vol. 2, ed. H. Harris and K. Hirschhorn, p. 61. Plenum Press, New York
- , NANCE, W. E., RAWLS, R. F., and WHITE, J. G. (1970) *Amer. J. hum. Genet.*, **22**, 55
- , NISWANDER, J. D., BERGSMAN, D. R., WORKMAN, P. L., and WHITE, J. G. (1972) *Amer. J. phys. Anthropol.*, **36**, 397