Journal of Medical Genetics (1970). **7**, 224.

Hereditary Macular Coloboma

C. I. PHILLIPS*

It is an honour to be asked to contribute a short review of this subject as part of a tribute to Professor Arnold Sorsby. It must give him particular pleasure to be the first editor of the *Journal of Medical Genetics*, a recognition of his great contribitions to Medicine as well as to Ophthalmology.

The term 'coloboma' is an unfortunate one because of the danger of confusion with the better understood defect in the retina and choroid extending downwards from the optic disc along with a notch in the crystalline lens and a cleft in the lower iris which often produces a downward-displaced or key-hole pupil. This combination is usually explained by failure in fusion of the foetal fissure. No such simple embryological explanation is available for these cases of macular coloboma (Fig. 1) in which an area at the macula of 3–6 disc diameters shows absent or rudimentary retina and choroid, so that sclera, often ectatic in the same area, can be seen ophthalmoscopically. When a *unilateral* macular 'scar' with or without pigmentation is found, in the absence of a positive family history or parental consanguinity, the diagnosis is usually healed toxoplasmic choroiditis (see Perkins, 1961) or healed chorioretinitis due to *Toxocara canis* or *cati* (see Ashton, 1960); such diagnoses are presumptive usually, and unless the examiner can be sure from previous observation on the same patient that the lesions are acquired, there remains a possibility of hereditary macular coloboma. On the other hand, when such lesions are bilateral and symmetrical, the chances are much greater that there is an hereditary explanation, which is made almost certain when other cases are seen in the same family, especially when other bizarre abnormalities are present in other systems. A sharp margin is the least unreliable sign suggesting an hereditary coloboma, and the greater the excavation the more the support for that explanation (Sorsby, 1935).

* Address: Department of Ophthalmology, Royal Eye Hospital, Oxford Road, Manchester M13 9WH.

Coloboma without Extraocular Involvement

Clausen (1921, 1928) seems to have been the first worker to record hereditary macular colobomata, with a dominant pattern (a father and his two sons; his sister and her two daughters). Less definite dominance was present in the family described by Schott (1921): two sisters, a paternal uncle, and probably some male cousins. A bilaterally affected mother and son were reported by Davenport in 1927. The affection in 5 sibs (4 females and 1 male) described by Evans (1937) was probably dominant, but the existence of similar defects in the mother and maternal grandfather was not definitely known; one female was unilaterally affected, which suggests that all unilateral macular colobomata need not be considered acquired in origin. Another unilateral case was recorded by Waardenburg (1938) in the grandson of the paternal uncle of a bilaterally affected male who had three bilaterally affected sons.

Coloboma with Extraocular Involvement

Sorsby achieved one of his many 'firsts' in 1935 when he described a family with dominantly inherited eye lesions along with an apical dystrophy of hands and feet. The mother was the only one affected of the total sibship in her generation of 11, of which 5 were males and 6, including herself, were females; there was no positive history of any similar condition in her grandparents or her father or mother who were not consanguineous and who died aged 72 and 68, respectively. She had 10 pregnancies of which III.2 and III.11 were miscarriages, and III.1 and III.9 were unaffected females. III.3 died aged 19 months. III.4 was an unaffected male. III.6–8 and III.12 were affected males (Fig. 2).

Each affected member had bilaterally symmetrical macular colobomata with up to 2 dioptres of excavation and a horizontal dimension of 5–6 disc diameters and a vertical of 3–4, with sharp margins. Pigmentation was variable and some choroidal vessels could be seen. Nystagmus was present and the visual acuity was around 3/60 in all the affected ones.

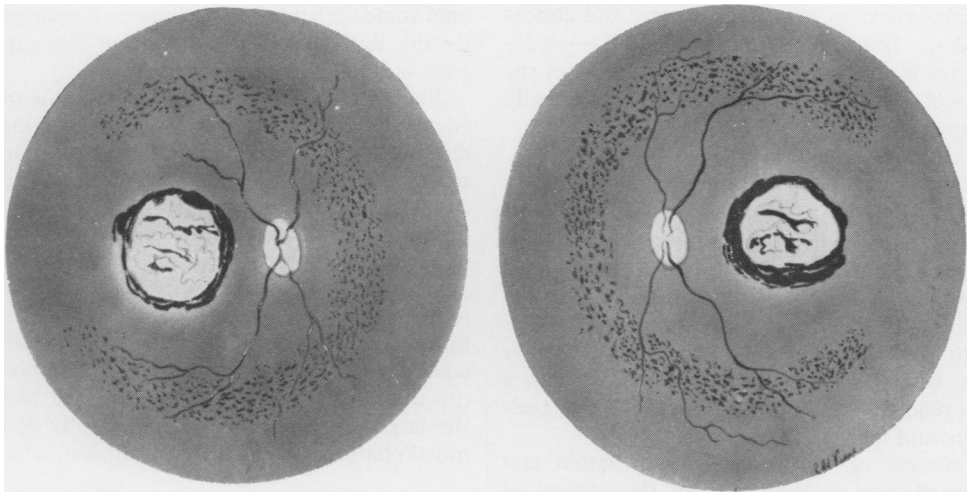

FIG. 1. Fundi of girl aged 16, showing bilateral macular colobomata and almost complete rings of lesions resembling those of pigmentary degeneration of the retina. The lesions showed much excavation (from Phillips and Lloyd Griffiths, 1969).

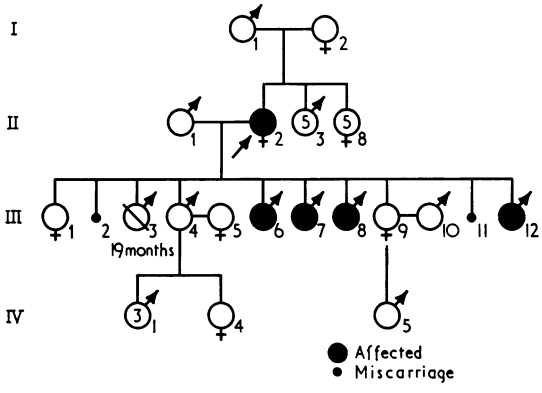

FIG. 2. Pedigree constructed from data recorded by Sorsby (1935). Family with macular colobomata and skeletal abnormalities. (Note: birth order of IV. 1–4 not known).

In addition to these ocular abnormalities, all the affected patients shared the following:

(a) Rudimentary or absent nails on the index finger of each hand and on the big toe of each foot.

(b) A wide terminal part of the big toe and a variable amount of similar abnormality in the thumb, which in III.6 was manifested as complete bifurcation of the thumb.

(c) Skeletal defects revealed on radiographs: (i) tendency to diminution or suppression of the second phalanx of the little finger, (ii) tendency to bifurcation of the terminal phalanx of the thumb, (iii) bifurcation in all but III.6 of the terminal phalanx of the large toe, (iv) tendency to atrophy of the terminal phalanges of both hands and feet.

Other abnormalities not shared in this family were complete absence of the right little toe in III.6, and absence of one kidney in III.7.

As Sorsby pointed out, this family's extra-ocular lesions were similar to the abnormalities in the dominantly inherited syndrome of apical dystrophy described by MacArthur and McCullough (1934).

By 1961, Waardenburg, Franceschetti, and Klein had found no mention in the literature of any syndrome like that described by Sorsby. However, in 1969, Phillips and Griffiths described a brother and sister who had macular colobomata, and hypermetropia with nystagmus, cleft palate, flexion deformity of the distal interphalangeal joints of both little fingers, and bilateral hallux valgus. Though the male had no other significant abnormalities, the girl, aged 16 years when examined, was mentally and physically retarded, had bilateral genu valgum which required tibial osteotomy and bilateral coxa valga and extremely small feet (15 cm. long). Negative findings of some importance were normal chromosomes, no consanguinity of parents, and no evidence of similar trouble in a large family tree of both parents. This pattern of heredity suggests that a recessive gene is probably responsible. However, the similarity of the lesions to those in the family described by Sorsby in which dominance was likely might favour the possibility that a mutation in one of the parents has introduced a dominant gene into the family. The study of more affected families may clarify the problem.

Very few other published accounts appear of an association between macular colobomata and extra-ocular abnormalities, but none of them resemble the above syndromes: Car (1925)—microcephaly, large

ears, thick wrists, 'pearl-string' fingers, and abnormally short little fingers; Clarke (1927)—undescended testis and 'bad development of most of the facial bones'; Feilchenfield (1911)—abnormally prominent ears.

Discussion

The description and taxonomy of hereditary abnormalities are intrinsically interesting and important, and allow us at least to impart invaluable information and advice to our patients. This aspect of medical work is of increasing value as our ability to prevent the deaths of patients, especially children, becomes greater; our responsibility to a patient's relatives and unborn children is being realized more and more.

The success of widespread immunization and later the efficacy of antibiotics in the control of infectious diseases have made us increasingly aware of the importance of inherited diseases. It is hardly surprising that many of the important discoveries which are occurring in biology relate to genetics—for example abnormalities of chromosomes, Lyonisation of the X chromosome, the existence of somatic mutations, and, of course, most fundamental of all, Watson and Crick's discovery of the genetic code.

The highly specific chemical abnormalities presumably underlying hereditary conditions are a tremendous challenge to research but at the same time provide the hope, or indeed the expectation, that selective specific preventive or even curative treatment can ultimately be achieved.

Summary

A macular coloboma is an area of 2–6 disk diameters in which there is total or considerable chorio-retinal maldevelopment, often with ectasia of the underlying sclera which produces the white appearance visible ophthalmoscopically. The differential diagnosis includes acquired choroido-retinitis, especially due to toxoplasmosis and larval toxocariasis, but almost all bilaterally symmetrical (and some unilateral) cases have an hereditary basis, usually dominant; the lesions are difficult to explain on grounds of maldevelopment.

There are very few recorded cases with extra-ocular abnormalities, and the most striking is the dominant rarity recorded first by Sorsby in which macular colobomata were accompanied by an 'apical dystrophy', i.e. rudimentary nails on the index finger of each hand and the big toe of each foot, a wide terminal part of the big toe, and a variable amount of similar abnormality in the thumb and, on radiographs, a tendency to diminution or suppression of the second phalanx of the little finger, tendency to bifurcation of the terminal phalanx of the thumb, bifurcation of the terminal phalanx of the large toe, and tendency to atrophy of the terminal phalanges of both hands and feet.

References

Ashton, N. (1960). Larval granulomatosis of the retina due to *toxocara*. *British Journal of Ophthalmology*, **44**, 129–148.

Car, A. (1925). Mikrozephalie und beiderseitiges Kolobom im Bereiche der Makula. *Zeitschrift für Augenheilkunde*, **57**, 618–627.

Clarke, E. (1927). Coloboma at the macula (both eyes). *British Journal of Ophthalmology*, **11**, 97–99.

Clausen, W. (1921). Typisches, beiderseitiges hereditäres Makula-Kolobom. *Klinische Monatsblätter für Augenheilkunde*, **67**, 116.

—— (1928). Zur Frage der Vererbung der Makulakolobome. *Klinische Monatsblätter für Augenheilkunde*, **81**, 385.

Davenport, R. C. (1927). Bilateral 'macular coloboma' in mother and son. *Proceedings of the Royal Society of Medicine*, **21**, 109–110.

Evans, P. J. (1937). Familial macular colobomata. *British Journal of Ophthalmology*, **21**, 503–506.

Feilchenfeld, H. (1911). *Zentralblatt für praktische Augenheilkunde*, **35**, 68.

MacArthur, J. W., and McCullough, E. (1932). Apical dystrophy. A inherited defect of hands and feet. *Human Biology*, **4**, 179–207.

Perkins, E. S. (1961). *Uveitis and Toxoplasmosis*. Churchill, London.

Phillips, C. I., and Griffiths, D. L. (1969). Macular coloboma and skeletal abnormality. *British Journal of Ophthalmology*, **53**, 346–349.

Schott, K. (1921). Über das soggenannte Kolobom der Makula. *Klinische Monatsblätter für Augenheilkunde*, **67**, 415–424.

Sorsby, A. (1935). Congenital coloboma of the macula: together with an account of the familial occurrence of bilateral macular coloboma in association with apical dystrophy of hands and feet. *British Journal of Ophthalmology*, **19**, 65–90.

Waardenburg, P. J. (1938). Einige Beobachtungen bei erblichen Augenabweichungen. *Klinische Monatsblätter für Augenheilkunde*, **101**, 924–925.

——, Franceschetti, A., and Klein, D. (1961). *Genetics and Ophthalmology*, vol. I, p. 788. Blackwell, Oxford.