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Hereditary Affections of the Retina and Choroid

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THE RANGE OF HEREDITARY ANOMALIES

Three fairly clear-cut groups of affections are met as hereditary disorders of the retina and choroid: congenital defects, the abiotrophies and tumours. Clinically the characteristic feature of the hereditary congenital defects is their obvious presence at birth; in contrast, the abiotrophies are hereditary affections that become manifest at some period of post-natal life, the tissue having functioned apparently normally until then; the status of hereditary tumours — exemplified by the retinoblastomata — is uncertain, for it is not known whether affected infants have in fact not been born with a minimal tumour.

Experimental and clinical studies on hereditary retinal and choroidal disorders have brought considerable clarification on the nature of hereditary disorders generally. Ophthalmologists have been particularly concerned with the abiotrophies (as they are known in English-speaking countries, though elsewhere the appellation of heredo-degenerative disease is preferred).

The place of the abiotrophies amongst the genetic disorders

The abiotrophies were so designated in 1902 by Sir William Gowers, who stressed that these disorders began in apparently healthy people and that many of the features are suggestive of premature senescence of the tissue — a view that recalled an earlier teaching of Sir James Paget at the middle of the last century. The designation of abiotrophy was introduced to emphasize an assumed lack of vitality in a tissue otherwise normal. There are therefore metaphysical implications in the term abiotrophy that are lacking in the more descriptive designation of heredo-degenerative affections. This latter designation, whilst preferable on most grounds, is however rather cumbersome, and the term abiotrophy, which appears to be too widely used to be readily displaced, has the advantage of brevity and as such is useful provided its aetiological implications are ignored. The term dystrophy is probably best, but by usage is limited to individual affections rather than to the general concept.

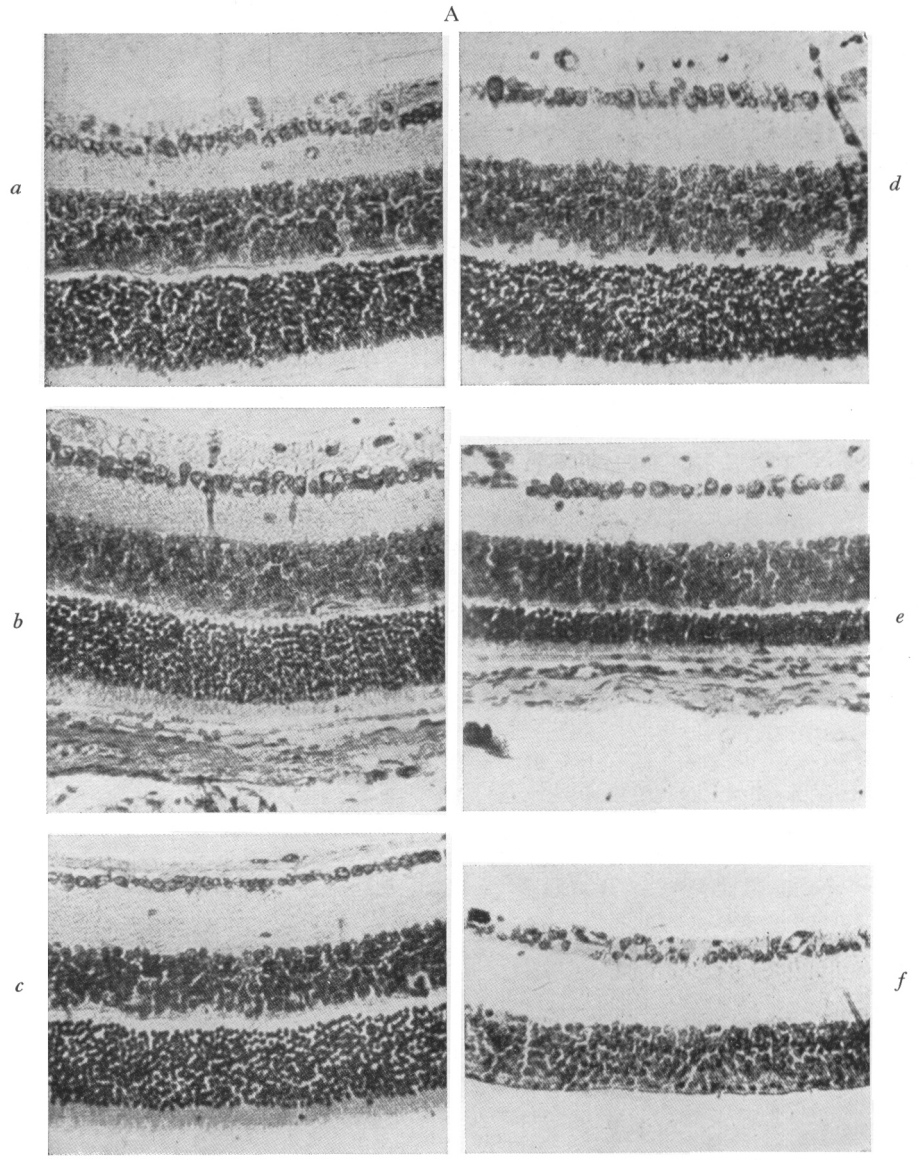
Classical examples of the abiotrophic lesions are retinitis pigmentosa in ophthalmology, some of the muscle dystrophies and Friedreich's ataxia in neurology, and Huntington's chorea in neuropsychiatry. All these disorders are hereditary and

begin in post-natal life after an apparently normal development in childhood or in adult life, the age of onset being different for different affections and sometimes for apparently the same disorder in different families.

The widespread assumption that the abiotrophic tissue is indeed normal until the affection sets in obtained some experimental support in a study by Bourne, Campbell and Tansley in 1938. These observers investigated in the rat a disturbance of the retina having the histological features of human retinitis pigmentosa, and showed that the retina had developed and become differentiated into its various layers in individuals of the affected stock before the degenerative process set in. This reading is, however, no longer accepted. In 1954 it was shown that differentiation of the retina into its various layers was not evidence of full normal development (Sorsby, Koller, Attfield, Davey and Lucas). In a strain of mice with retinal dystrophy these observers found that whilst the rod layer was laid down as such in affected animals, it never developed normally but showed degenerative changes before reaching complete differentiation and normal size, i. e., the rods were in fact merely primitive rods, and normal post-natal development had been replaced by degenerative changes. These changes are shown in Fig. 1. The same workers recorded similar findings in the Irish setter and in the rat (Lucas, 1954; Lucas, Attfield and Davey, 1955), the study on the rat having special interest in that the same strain was used as was studied by Bourne and her colleagues in 1938. These observations on the primitive character of the rods in affected strains of rats and mice have been confirmed by other observers (Tansley, 1954; Noell, 1958 and others). On this reading it is clear that there is no fundamental difference between a congenital defect and an abiotrophic affection. In the congenital defect the hereditary anomaly has run its course in intrauterine life, whilst in the abiotrophic disturbance normal post-natal development is lacking or faulty and is replaced instead by a hereditarily determined degeneration. This unification of hereditary congenital defects and abiotrophic disorders is borne out by the fact that not all congenital abnormalities are indeed stationary and non-progressive (as will be seen in the description given below of congenital macular cysts and suchlike disorders) whilst some abiotrophic defects are only mildly progressive. The congenital defect presents as a morphological defect, and the abiotrophic disorder is recognised whilst it is stile a histological defect; the first is often stationary, the second is always progressive to some degree; both are present at birth.

That a sharp contrast between congenital hereditary disturbances and abiotrophic disorders is artificial is also borne out by such disorders as the phakomatoses, the retinoblastomata, and the occasional hereditary sarcomata of the choroid. In these disorders, some of which become manifest in childhood and others in adult life, an obvious congenital anomaly of a minor character is often present at birth — almost always in the phakomata and probably also in retinoblastoma.

Fig. 1. 'Abiotrophy' as a failure in final differentiation of a tissue, illustrated by the sequence of development in recessive retinal dystrophy of the retinitis pigmentosa type in the mouse



A. Postnatal development of the normal retina is contrasted to that of the retina in the affected strain. At birth the retina consists of a cellular mass, which does not become differentiated into layers till the 11th day. By then the different layers of the adult retina are clearly seen.

a), *b*) and *c*) In the normal retina the rod and outer nuclear layers continue to develop to reach full maturity by about the 28th day. *d*), *e*) and *f*) In the affected strain development is normal till differentiation into layers occurs (*d*), but subsequently the rod and outer nuclear layers fail to develop and quickly degenerate (*e* and *f*).

Normal	At	Affected
(*a*)	11 days	(*d*)
(*b*)	14 days	(*e*)
(*c*)	28 days	(*f*)

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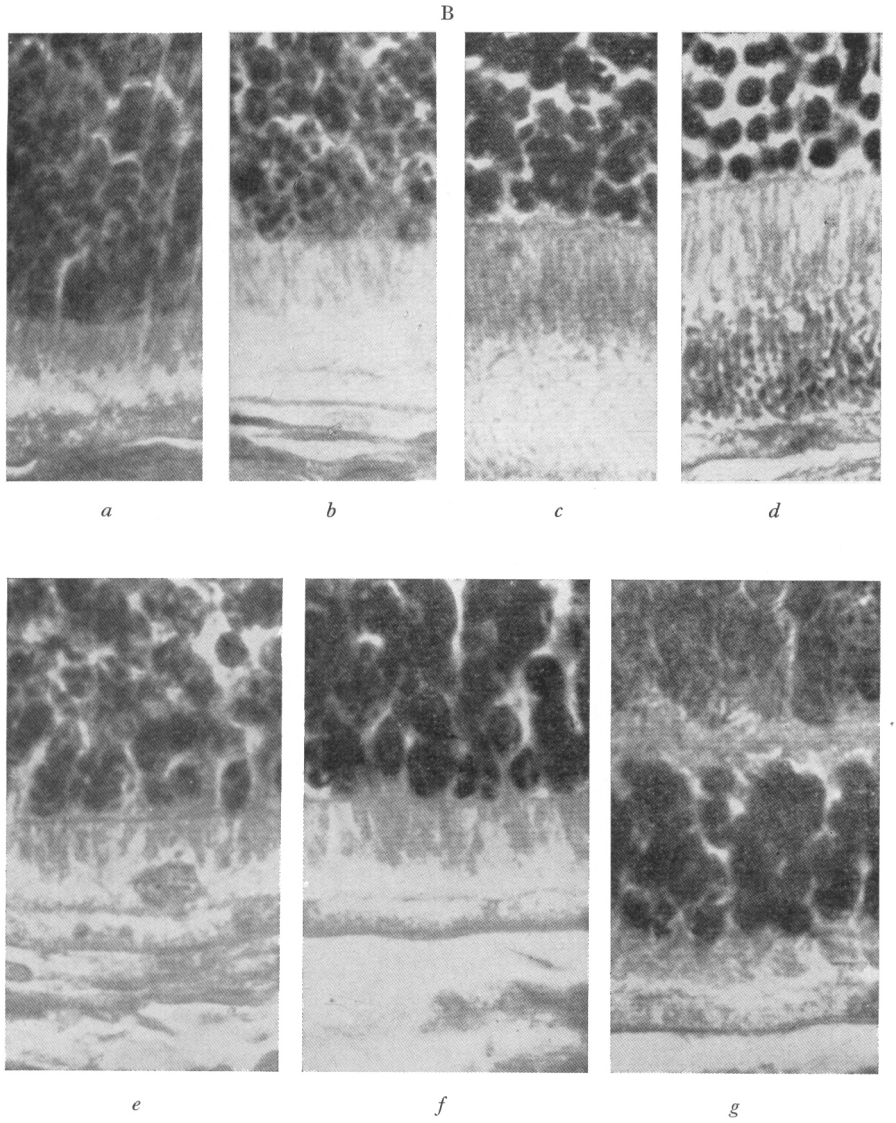
Fig. 1 *(continued)*



B. High power views of the changes recorded in A.
a), *b*), *c*) and *d*) Development in normal mouse at 12, 14, 21 and 28 days. Note that whilst rod and nuclear layers are already differentiated at 12 days after birth, there is considerable postnatal development so that at 28 days the rods are clearly differentiated into 2 segments.
e), *f*) and *g*). Development in affected mouse at 11, 13 and 14 days. Note that in contrast to normal postnatal development beyond the 11th or 12th day, there are rapidly developing regressive changes in the rods. At 28 days, when normal retina has reached full development, rods and outer nuclear layers in the affected mouse are completely degenerate (After A. Sorsby, P. C., Koller M. Attfield, J. B. Davey, and D. R. Lucas, 1954. J. exp. Zool., 125, 171)

The polymorphic appearances of the abiotrophies

In one respect the distinction between congenital and abiotrophic defects is of immense value clinically. The congenital defect, which generally has little or no significant post-natal development, shows a fairly characteristic appearance which varies but slightly from patient to patient. In contrast, the abiotrophic defect is frequently polymorphous, and the different stages of development frequently show marked differences, not readily recognized as different stages of one and the same affection. The abiotrophic disorder has not one face, but many. Recognition of the polymorphic character of these affections has greatly facilitated diagnosis of fundus lesions, for in the past many intermediate aspects of the fundus dystrophies were confused with inflammatory and other disorders of environmental origin.

II. CONGENITAL ANOMALIES

Three types of congenital defect can be distinguished. The least common is that caused by arrested embryological development. Typical choroidal coloboma is illustrative, and the range of appearances is determined by the degree of secondary degenerative changes, which may extend to cyst formation and 'anophthalmos'. Fig. 2 shows how arrested development can lead to extensive secondary changes. In man these changes would occur in intrauterine life. More commonly congenital defects are the result of an anomalous development, the nature of which is obscure. Macular coloboma is illustrative of this group, and as the disorder has run the whole of its course in intrauterine life, there is a congenital stationary defect. Sometimes, as with sex-linked cystic detachment of the retina, dominant macular cyst, and with retinal aplasia there is not only a congenital defect, but a considerable post-natal course, so that the defect is both congenital and progressive — a transition, as already noted, to the abiotrophies.

Retina

Opaque nerve fibres

Most cases are unilateral and appear to be sporadic. Opaque nerve fibres have been seen in monovular twins, in whom discordant findings have also been reported. There is considerable variation in expression of the gene for bilateral cases are exceptional. Chart 1 suggests dominant inheritance. Pedigree showing affected sibships only might possibly illustrate irregular dominance.

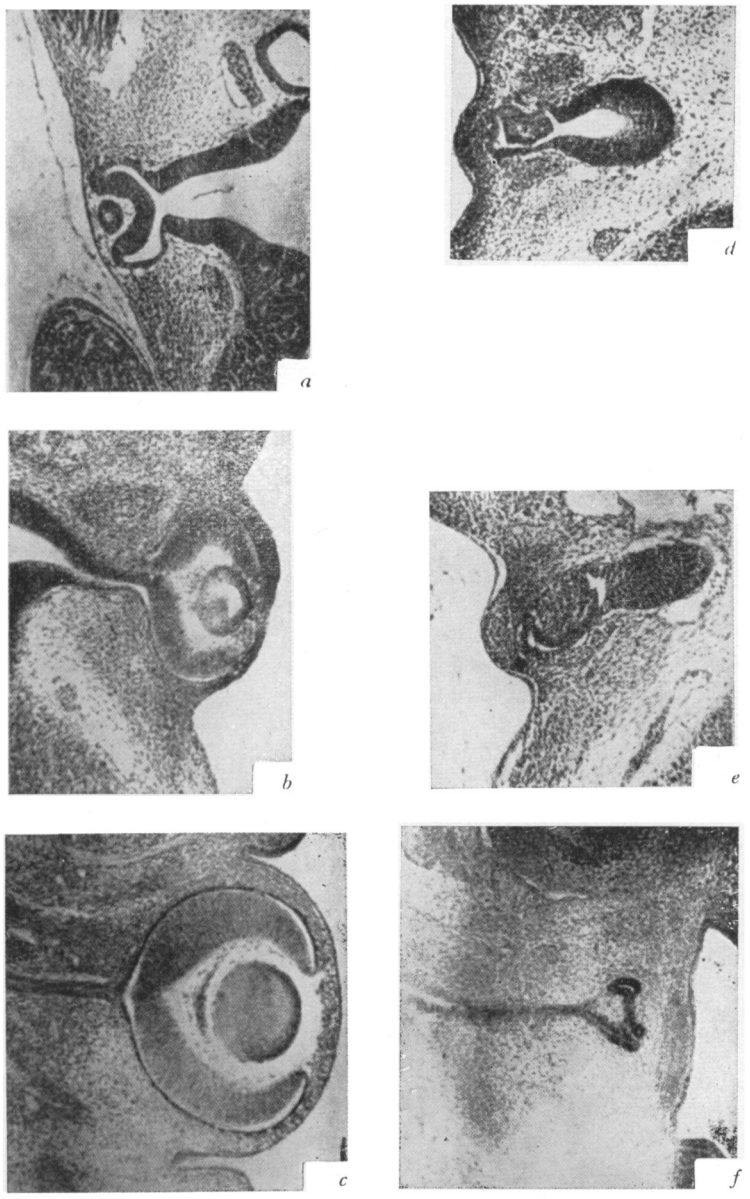


Fig. 2. Congenital defect: hereditary anophthalmos in the mouse consequent on disturbance in development. At 10 days the normal and affected strains show fairly similar stages of invagination of the optic vesicle. Subsequently degenerative changes set in the affected strain instead of normal development
(After Chase H. B., and Chase E. B., 1941. J. Morph., 68, 279)

Control	Anophthalmic strain	
a) Left eye	*d*) Left eye	*a*) and *d*) at 10 days 23 hours
b) Right eye	*e*) Left eye	*b*) and *e*) at 11 days 20 hours
c) Right eye	*f*) Right eye	*c*) and *f*) at 13 days 2 hours

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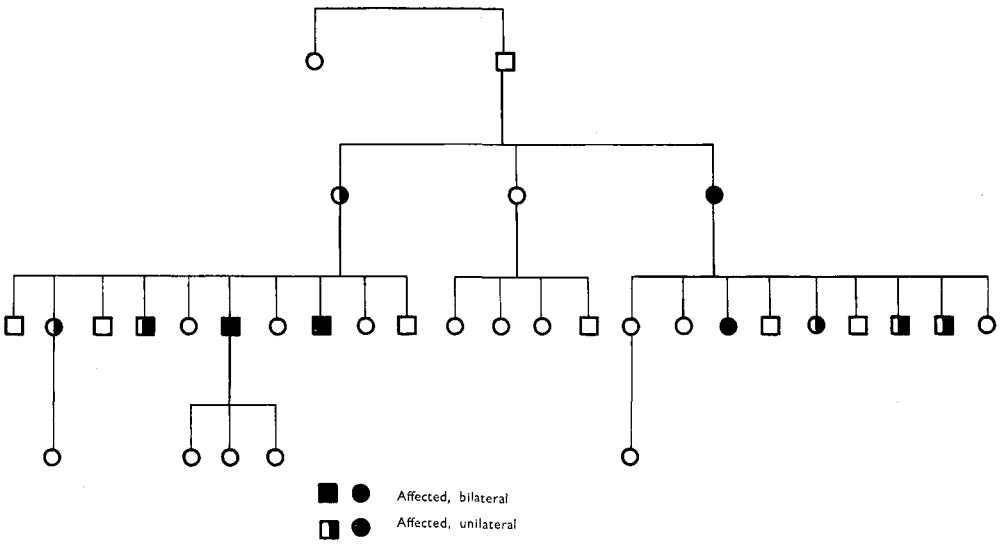


Chart 1. Opaque nerve fibres. Pedigree over two generations (After E. A. Cockayne, 1936 Brit. J. Ophthal. 20, 569)

Congenital macular defects

Three congenital macular defects (apart from macular coloboma, discussed under choroid), have been recognized: Best's disease, congenital macular cyst, and asymptomatic macular lesions. All three are dominant and it is likely that Best's disease and macular cysts are not two distinct entities, but one and the same affection.

1) *Best's disease*

In 1905 Best described a family with macular lesions apparently congenital, sometimes central, sometimes paracentral, and often with good vision. This family has been studied subsequently by Weisel in 1922 and Jung in 1937, and it is fairly definite that this is a congenital anomaly with variable degrees of visual defect. It is not clear from the accounts whether macular cysts were present in these cases and if so whether they had burts later in life with deterioration in vision. Apart from the family recorded by Best in Germany, there is a study by Falls (1949) of an American family, but the diagnosis is not conclusive.

2) *Macular cyst*

Historical. Macular cysts have been recognized for many years as cysts or 'holes' at the macula. It has also been known that vision can be good with a macular 'hole'. That the affection is hereditary and shows a progressive course has been recognized only recently (Sorsby, Savory and Davey, 1956).

Clinical features. Macular cysts are in all probability congenital. Vision remains good until middle-age when these cysts tend to burst and irritative reactions set in at the central area with progressive loss of central vision. The families studied have all shown dominant inheritance (Chart 2*a*) though in one family the dominance was apparently irregular (Chart 2*b*) — the unaffected transmitter of the affection

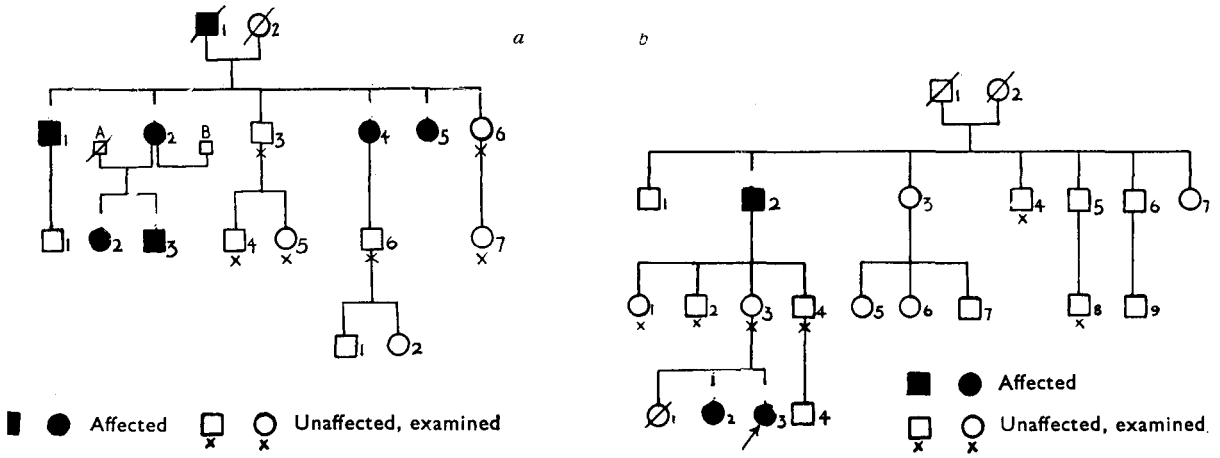


Chart 2. Macular cysts. *a*) Pedigree showing dominant inheritance. *b*) Pedigree showing irregular dominance (After A. Sorsby, M. Savory, J. B. Davey, and R. J. L. Fraser, 1956. Brit. J. Ophthal. 40, 144)

showing an uncharacteristic asymptomatic central lesion. Macular cysts therefore illustrate a group of affections which are apparently congenital in character and progressive in post-natal life. The range of ophthalmoscopic appearances is illustrated in Fig. 3. As already indicated, with a fuller recognition of the hereditary character of macular cyst and its progressive course, it may be questioned whether the cases recorded by Best do not fit into this group. Confusion with dominant macular dystrophy is unlikely on the ophthalmoscopic appearances.

3) *Asymptomatic macular defect*

Pedigree chart 3 illustrates the dominant transmission of an apparently congenital macular lesion, which opthalmoscopically (Fig. 4) could not be distinguished from the classical forms of macular dystrophy, but from which it differs in these two signif-

icant respects: 1) it is present early in life and is presumably congenital, and 2) in contrast to the macular dystrophies, there is no loss of central vision. These cases are probably rare, but they have to be borne in mind in the differential diagnosis of dominant macular dystrophy. Ophthalmoscopically the distinction may be impossible, whilst subjectively in the early stages of dominant macular dystrophy there is a macular lesion without substantial symptoms. At this stage the differential diagnosis can generally be established by the presence of anomalies of colour-vision in dominant macular dystrophy, but not in the asymptomatic lesion.

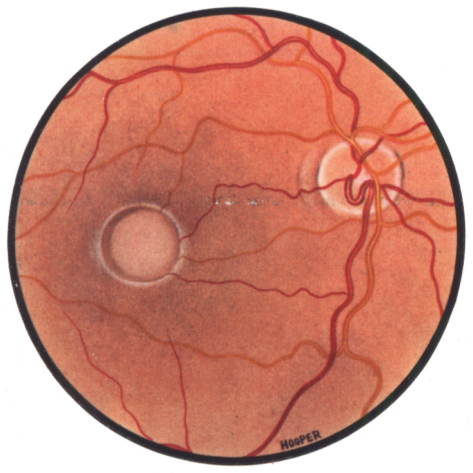
Retinal aplasia

Historical. That some infants are blind without any ophthalmoscopic lesion to account for it, has presented a considerable clinical problem for many years. Schilder's disease and the related Pelizaeus-Merzbacher affection explained some of these cases, but in infants without neurological symptoms there was no adequate answer. Designations like cortical blindness, amaurosis congenita, and the hypothesis of rodless retinae hardly take matters any further. In 1957, Alström and Olson showed that some 10 per cent of the inmates of blind schools in Sweden during the past half century could in fact be shown to have suffered from a congenital progressive disorder which they designated *heredoretinopathia congenitalis monohybrida recessiva autosomalis.* Family studies on the inmates revealed a progressive disorder extending from a fundus without any lesions to fundi with pepper and salt pigmentation, and later still to retinal atrophy with heavy pigmentation, optic atrophy and narrowing of the retinal vessels. The Swedish material suggested that the affection was recessive, and not uncommon once it was recognized that many children admitted on different diagnoses fell into one group. A confirmatory study from Holland (Schappert-Kimmijser, Henkes and van den Bosch, 1959) showed an even higher percentage of affected individuals in the Dutch blind schools. In Great Britain, Sorsby and Williams (1960) showed that the affection has a dominant as well as a recessive form.

Clinical features. The children are born apparently normal, but do not seem to develop normally as regards sight. Ophthalmoscopic examination is generally negative, though questionable optic atrophy is sometimes suggested. As the blindness becomes confirmed with increasing age, ophthalmoscopic changes become apparent (Fig. 5). These are progressive and the ultimate stage is one of 'atypical retinitis pigmentosa' or 'diffuse chorio-retinitis'. Gross pigmentary changes become obvious as does marked optic atrophy.

Keratononus and lens opacities occur with increasing frequency at the higher ages. In the Swedish series mental deficiency was not an outstanding aspect. In the dominant family seen in England, out of a sibship of 4 boys, two were affected with both retinal aplasia and gross mental defect.

Pathology. Adequate studies are not yet available. From the blindness it is clear that the retinal defect present at birth is extensive, though the fundi are apparently normal. Normal ophthalmoscopic appearances are of course consistent with an ill-



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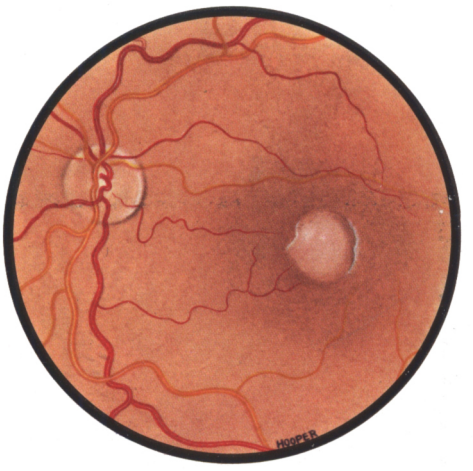

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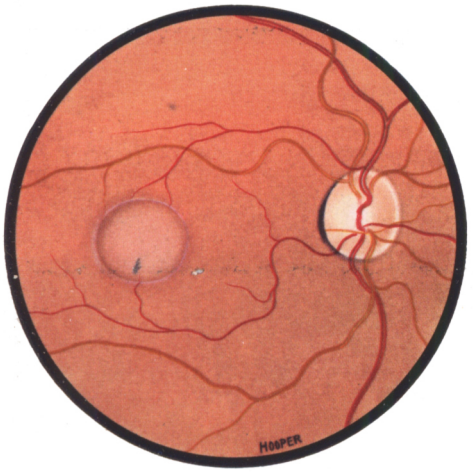

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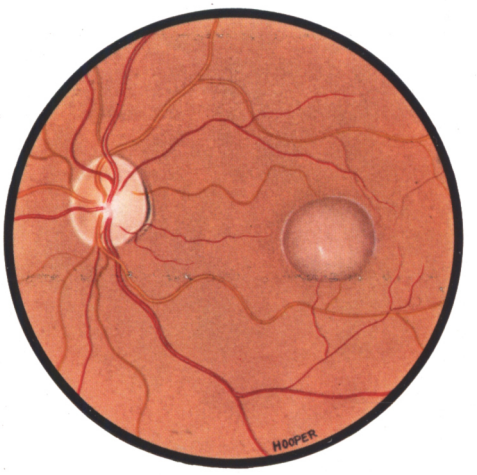

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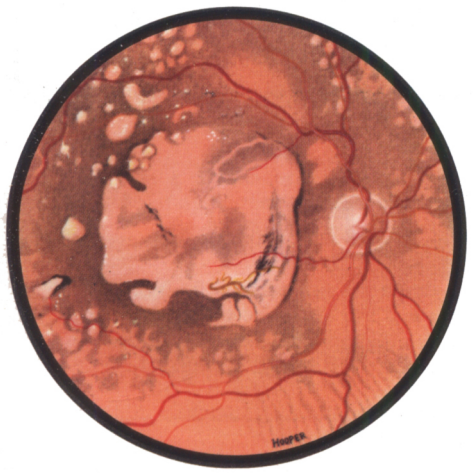

e

Fig. 3 A. Dominant congenital cyst at macula. Appearances over two generations.

a) and *b*). Right and left fundi of a man aged 43. Visual acuity: right 6/6, left 6/9 partly. Vision in the left eye had become blurred only lately. No central field defect, nor marked anomaly in colour vision. Left cyst probably ruptured.
c) and *d*). Right and left fundi of a younger sister aged 34. Visual acuity: right 6/6, left 6/9 partly, recently complicated by distortion of objects. Cysts intact.
e) Right fundus of their father, aged 79. Visual acuity: 6/60 in each eye.
(After Sorsby A., Savory M., Davey J. B. and Fraser R. J. L., 1956. Brit. J. Ophthal. 40, 144)

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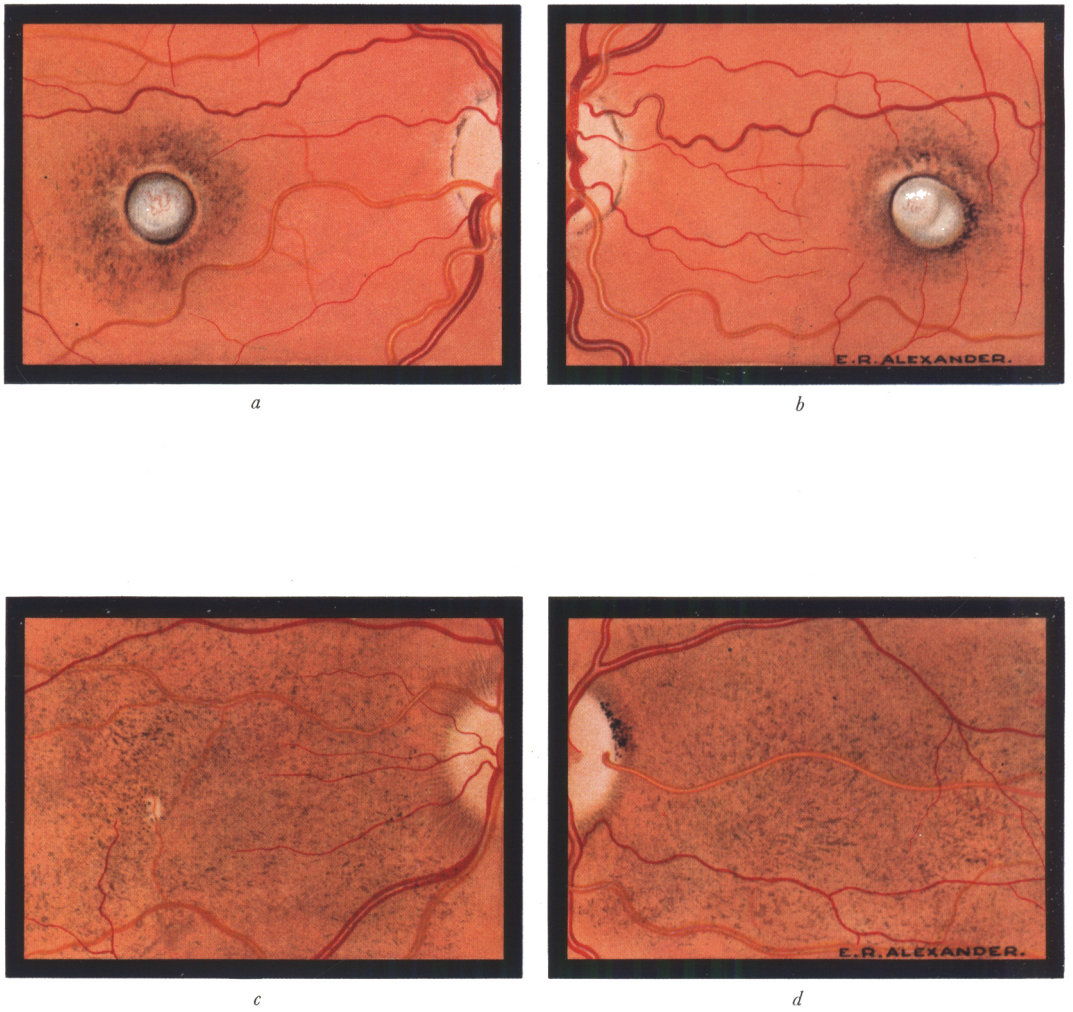

a *b*

c *d*

Fig. 3 B. Dominant congenital cyst at macula. Typical lesion in a girl aged 14 and abortive appearances in her mother.

a) and *b*). Right and left fundi of a girl at the age of 14. Visual acuity: right 6/9 partly, left 6/12 partly. This girl at 17 had been under observation for some 10 years and had shown no substantial changes.

c) and *d*). Right and left fundi of her mother, aged 42. Vision full; diffuse mottling throughout posterior pole. (After Sorsby A., Savory M., Davey J. B. and Fraser R. J. L., 1956. Brit. J. Ophthal. 40, 144)

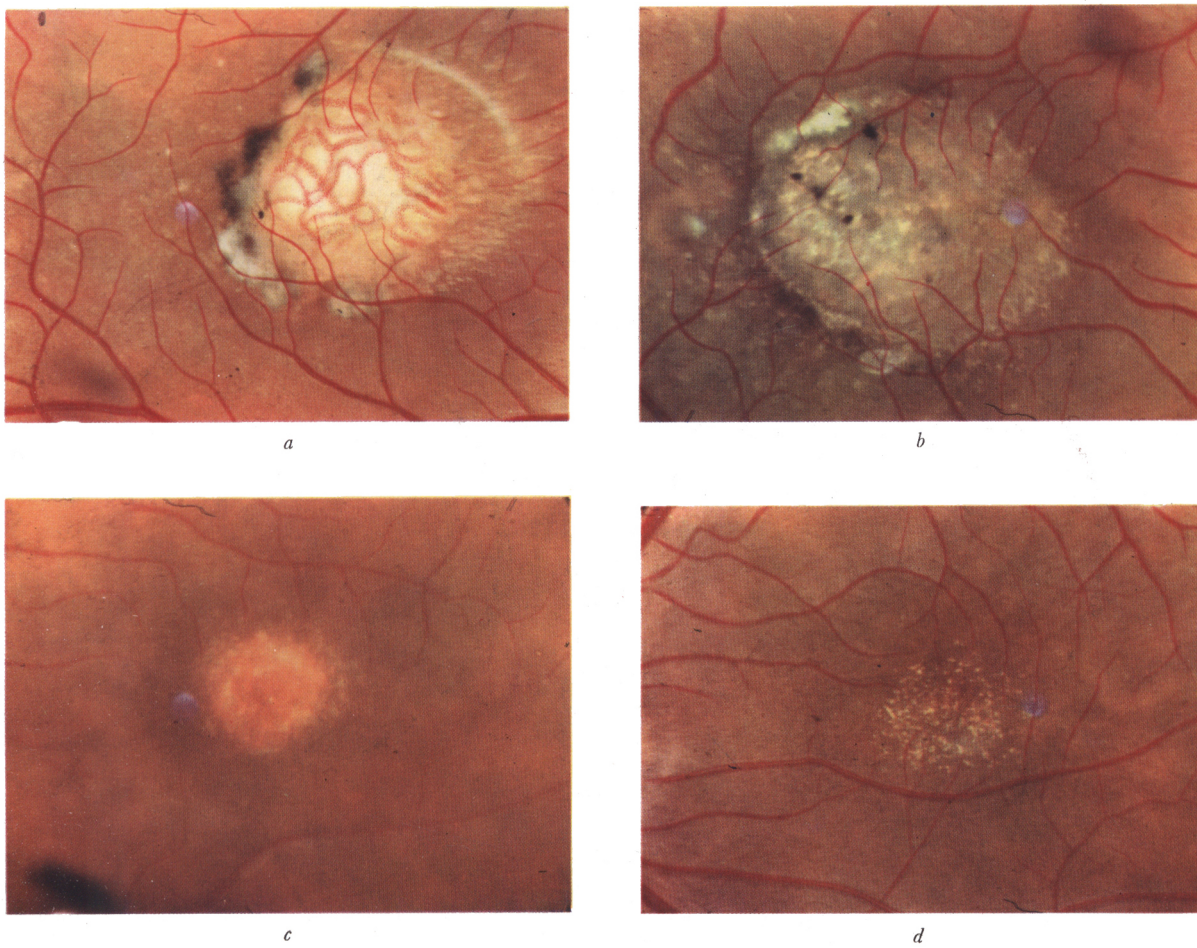

Fig. 4. Dominant asymptomatic macular defects. Appearances seen in two generations.
a) and *b*) Marked atrophic changes in a boy and his mother (III, 2 and II, 1 in Chart 3).
c) and *d*) Milder lesion in a brother and in their mother's sister (III, 1 and II, 4).
(After Sorsby A., and Wren N., 1960. A.M.A. Arch. Ophthal. 63, 918)

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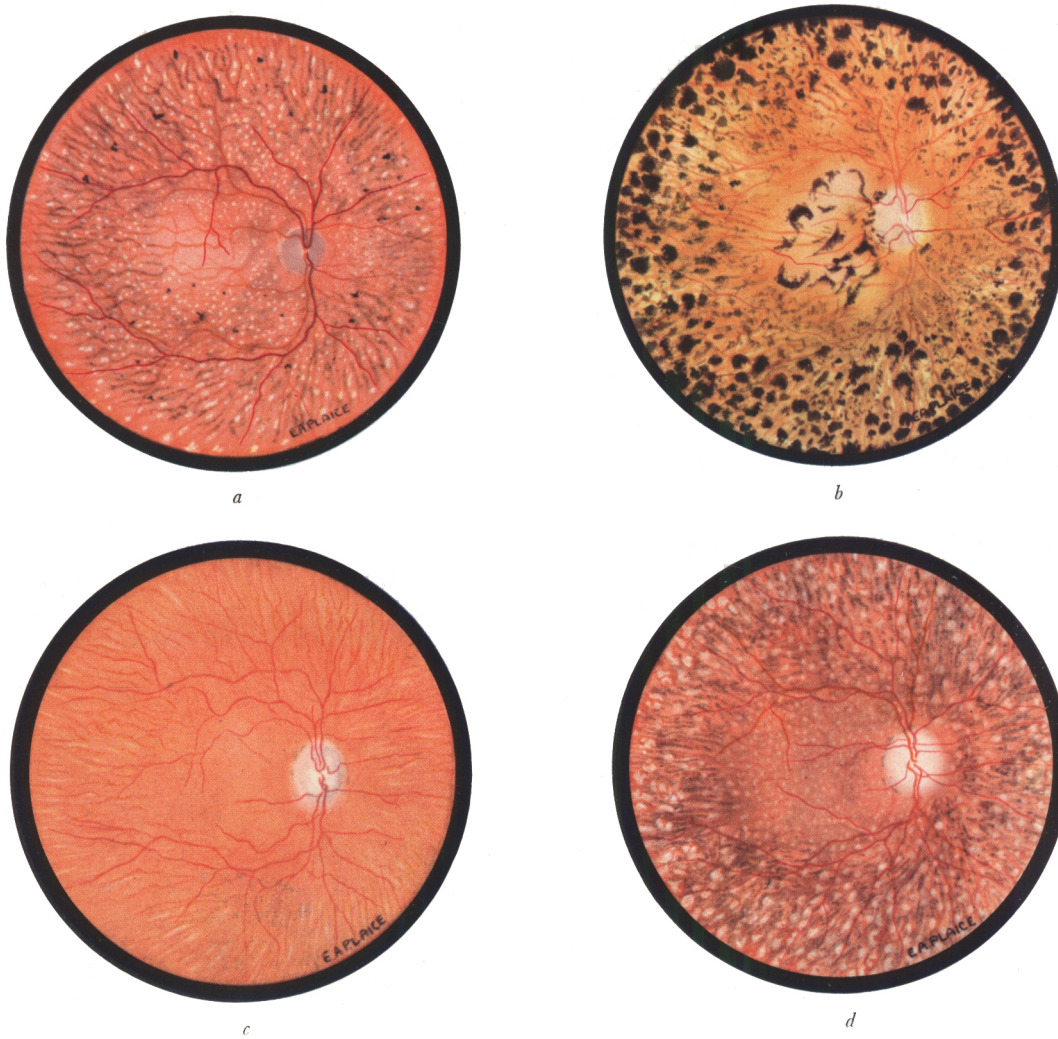

Fig. 5. Retinal aplasia.

a) and *b*) Appearances in a family showing the dominant form of the affection

a) The right fundus in a boy aged 9. The disk is grey, the arteries and veins are narrow, and the fundus background shows diffuse mottling of a crude pepper-and-salt type.

b) The right fundus of a woman aged 40, an aunt of the boy shown in *a*). In addition to advanced optic atrophy with marked narrowing of the retinal vessels, there is crude pigmentation scattered throughout the fundus with extensive areas of chorio-retinal atrophy.

c) and *d*) Appearances in a family with the recessive form of the affection.

c) The right fundus in a girl aged 19. There is marked optic atrophy, with fine pepper-and-salt changes throughout the fundus.

d) The right fundus in a younger sister of the patient shown in *c*). The fundus background shows the same advanced optic atrophy, and a considerably more obvious retinal atrophy is shown by the crude pepper-and-salt patterning. Note the essential similarity ophthalmoscopically of the two genetic types (After Sorsby, A. and Williams C. E., 1960. Brit. Med. J. i, 293)

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differentiated retina, and it is tempting to regard retinal aplasia as a more marked failure of retinal development than is seen in retinitis pigmentosa, in which functioning retina is present at birth.

In the one brain of a grossly mentally defective boy examined (Sorsby and Wil-

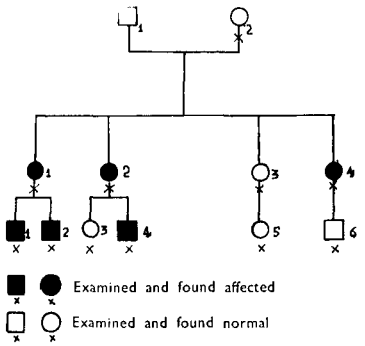

Chart 3. Asymptomatic macular defect. Pedigree showing dominant inheritance (After A. Sorsby and N. Wren 1960). A.M.A. Arch. Ophthal. 63, 918)

liams, 1960) there were no histological changes, so that there is a presumption that the mental deficiency is biochemical in nature rather than the more common type with morphological changes. The retina in this case showed extensive disorganization.

Heredity. As yet there is only one record of dominant inheritance in an affection that is commonly recessive (Chart 4*a-b*).

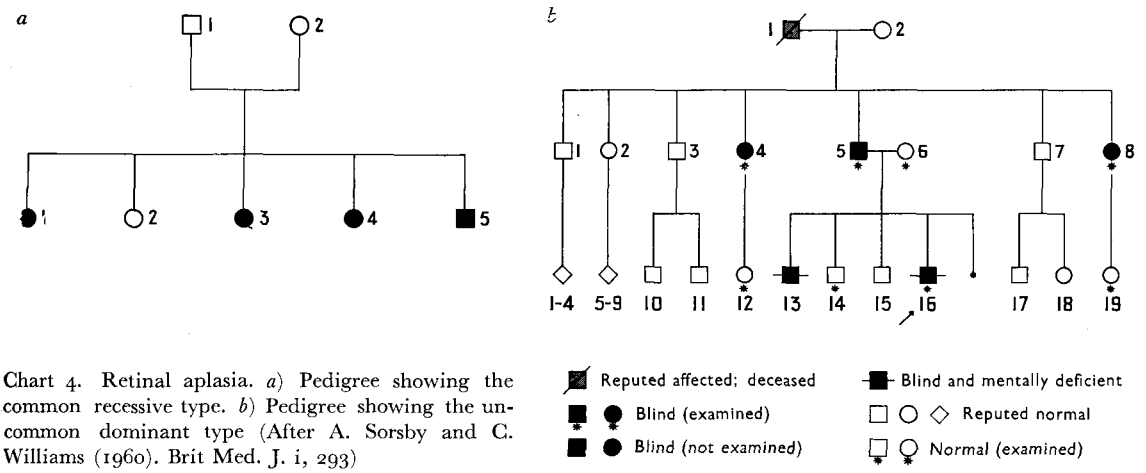

Chart 4. Retinal aplasia. *a*) Pedigree showing the common recessive type. *b*) Pedigree showing the uncommon dominant type (After A. Sorsby and C. Williams (1960). Brit Med. J. i, 293)

Macular aplasia

An ill-developed macula is assumed to underlie congenital day blindness (congenital total colour blindness) discussed elsewhere.

Congenital sex-linked retinoschisis

Historical. In 1935 Weve described falciform detachment of the retina, and Ida Mann vascular veils in the vitreous. It was thought at the time that these were different names for one and the same affection. Weve regarded falciform fold as a genetic anomaly as he had seen it in both members of a uniovular twin and had observed falciform fold and pseudoglioma in two brothers, a male cousin of whom also had pseudoglioma. Sorsby, Klein, Gann and Siggins (1951) showed that vascular veils in the vitreous were an aspect of a hereditary affection — congenital cystic detachment of the retina — which was sex-linked in its mode of inheritance, congenital in origin and progressive in character; they held that vascular veil in the vitreous was the anterior face of a ruptured cystic detachment. They also drew attention to sex-linked pseudoglioma or total detachment of the retina and suggested that falciform fold, congenital cystic detachment and congenital total detachment (pseudoglioma) are all different aspects of the same affection with some intra familial stability. The occasional case of falciform fold in girls is readily explained by the fact that such lesions are now known to occur with retrolental fibroplasia and even toxoplasmosis.

Clinical features. Congenital cystic detachment does not always present as a cyst; more commonly there are characteristic sharp edges of what look like multiple disinsertions, and it is likely that at an earlier stage there were multiple cysts which have ruptures, and that the sharp edge is merely part of the torn anterior surface. In a ruptured cyst it occasionally happens that the anterior surface with its retinal vessels floats forward giving the appearance of vascular veils in the vitreous. Apart from bursting and producing vascular veils, haemorrhage may occur into the cyst leading to the appearance of a tumour. The end stage shows a fundus lesion indistinguishable from a diffuse chorioretinal inflammation. The wide range of appearances in one family is shown in Fig. 6.

Sex-linkage (Chart 5) helps in establishing the diagnosis: the female carriers do not apparently show any diagnostic features.

Choroid

Macular coloboma

This is the one well established hereditary choroidal defect present at birth (apart from atypical coloboma of the choroid, which is part of the larger picture of colobomatous defects generally and is discussed elsewhere). The term macular coloboma is, however, descriptive of a variety of clinically distinct affections. Many, possibly most, macular colobomata are inflammatory in origin — heavy pigmentation being particularly suggestive — whilst associated calcified lesions towards the periphery of the fundus are characteristic of toxoplasmosis infection. The status of the rare nonpigmented ectatic coloboma is uncertain, but moderately pigmented macular

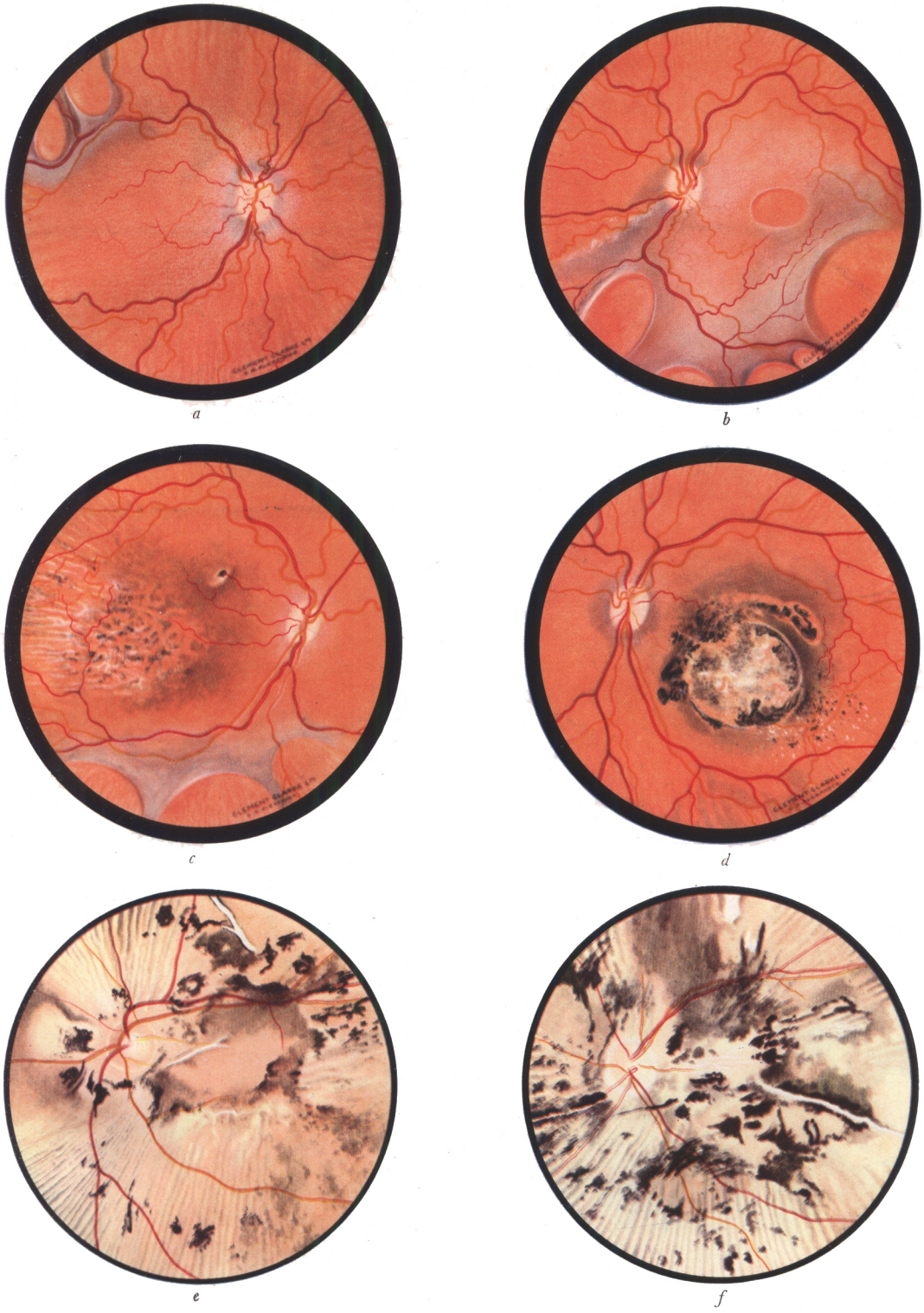

Fig. 6. Sex-linked congenital cystic retinal detachment (retinoschisis).
a) and *b*) show typical features seen in a man aged 30 years.
c) and *d*) illustrate the uncommon central pigmentary reactions seen as a complication in the right eye *c*), and as the exclusive lesion in the left eye *d*) in a younger brother, aged 25 years.
e) and *f*) illustrate the end stage of extreme chorioretinal atrophy seen in two maternal uncles aged 51 and 60 years respectively
(After Sorsby A., Klein M., Gann J. H., and Siggins G., 1951). Brit. J. Ophthal. 35, 1)

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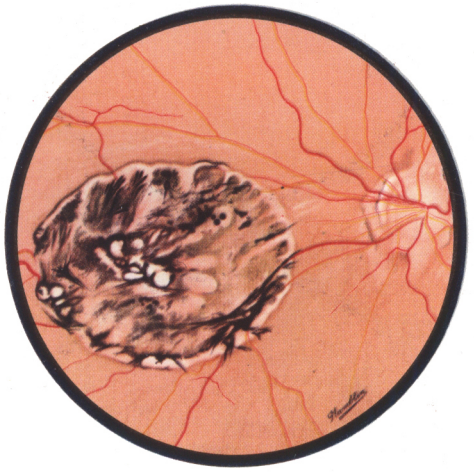

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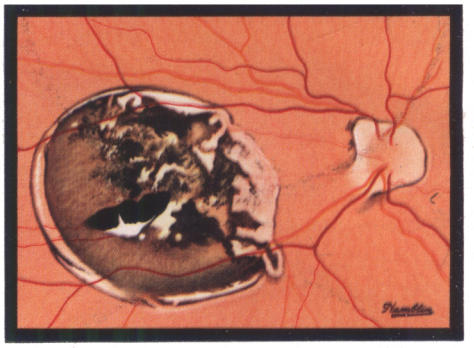

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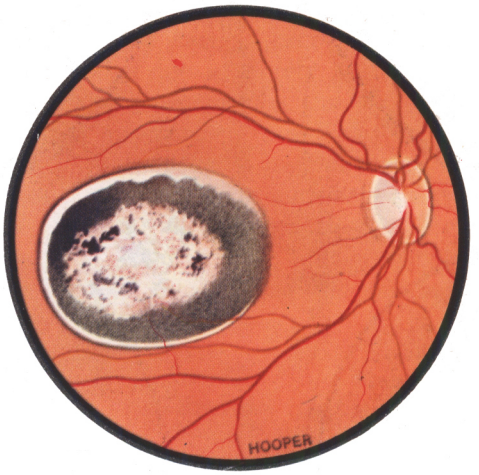

c

Fig. 7. Pigmented macular coloboma inherited over three generations.
a) Appearances in a woman (at the age of 58 years) the mother of 5 affected and 2 normal children.
b) Appearances in her son (drawn when he was 16).
c) Appearances in his daughter at the age of 8.
(After Sorsby A., 1935. Brit. J. Ophthal. 19, 65 and subsequent observation)

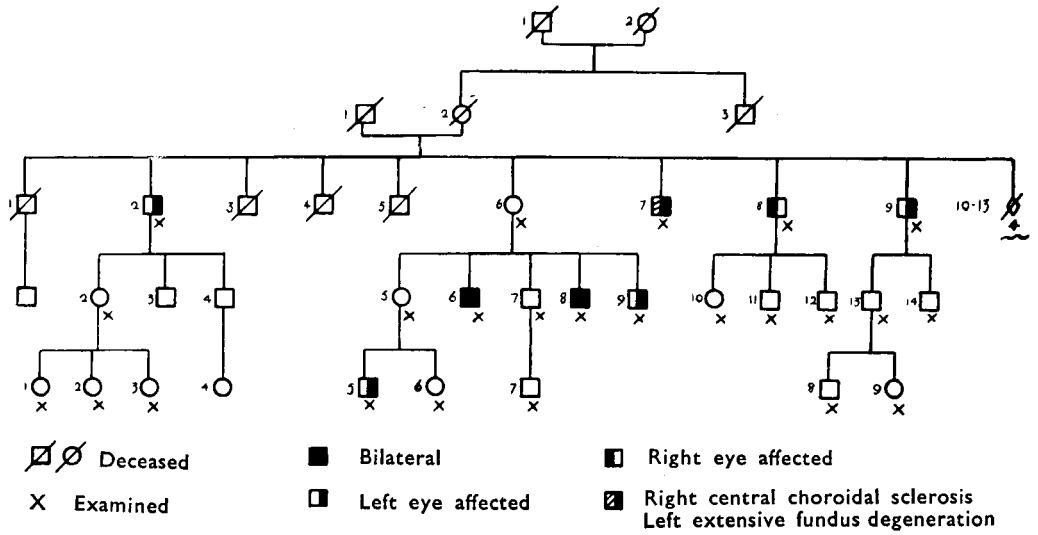

Chart 5. Congenital cystic retinal detachment. Pedigree of family illustrated in Fig. 6, showing sex-linkage and variable expression of the affection (After A. Sorsby, M. Klein, J. H. Gann, and G. Siggins, 1951. Brit. J. Ophthal., 35, 1)

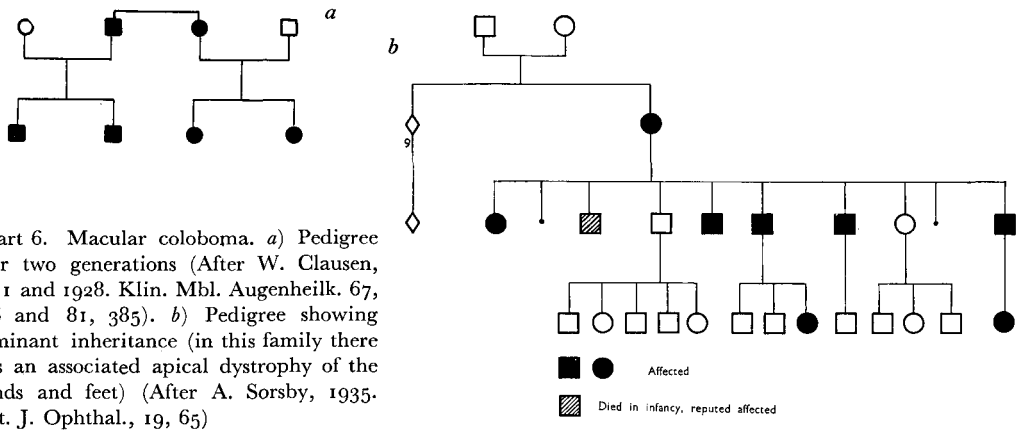

Chart 6. Macular coloboma. *a*) Pedigree over two generations (After W. Clausen, 1921 and 1928. Klin. Mbl. Augenheilk. 67, 116 and 81, 385). *b*) Pedigree showing dominant inheritance (in this family there was an associated apical dystrophy of the hands and feet) (After A. Sorsby, 1935. Brit. J. Ophthal., 19, 65)

colobomata (Fig. 7) are frequently hereditary in character. Macular coloboma has been observed in both members of a uniovular twin pair, and several times over two generations and once over three generations (Chart 6*a* and *b*).

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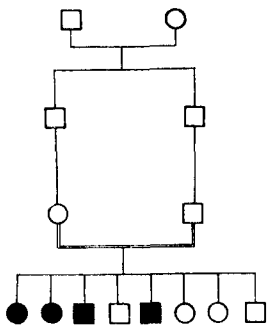
III. ABIOTROPHIC DISORDERS

The classical forms of abiotrophic affections of the retina are retinitis pigmentosa and macular dystrophy. Less common abiotrophic affections are gyrate atrophy of the retina and choroid, choroideremia, and the affection known as Doyne's choroiditis. Retinitis pigmentosa has a characteristic pigment reaction, and while the lesion in macular dystrophy is also pigmentary, there is mottling and atrophy instead of bone corpuscle reaction. In gyrate atrophy the reaction is almost entirely one of atrophy with exposure of white sclera. In choroideremia, fundamentally the same reaction is present, but on a more extensive scale with occasional bone corpuscle pigment. In Doyne's choroiditis, pigment proliferation is present, but in addition there are whitish 'exudates', or possibly large colloid bodies. In all these affections the reaction is, therefore, essentially one of atrophy and relatively fine pigmentary disturbances, except that in Doyne's choroiditis an approach to an exudative reaction is observed.

In recent years a considerably wider range of reactions has come to be recognized in the abiotrophic lesions. Angioid streaks with the not infrequently associated haemorrhages and exudates bear no similarity to the classical reactions. In choroidal sclerosis the conversion of the choroidal vessels into white streaks is yet another unusual abiotrophic reaction. Still more striking are the exudative reactions recorded in macular dystrophy, whilst in generalized fundus dystrophy oedema, haemorrhages and exudates can be observed in the early stages and massive pigmentary proliferation in the late stages.

The variety of abiotrophic reactions is therefore so wide as to simulate almost any type of fundus reaction traditionally associated with affections of environmental origin. These developments have extended the range of abiotrophic lesions to considerably beyond the limited range of affections recognized in the past.

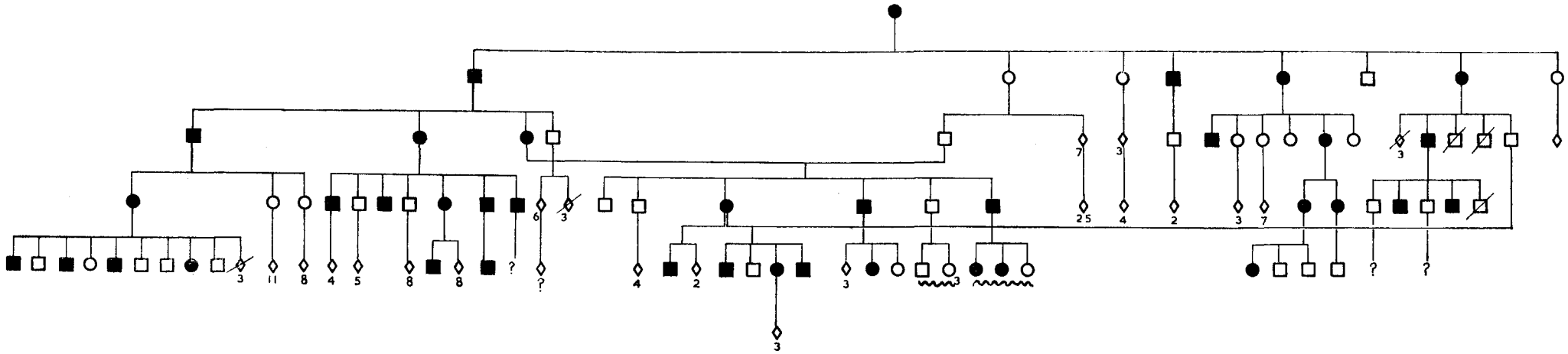
In retinitis pigmentosa it has been known for many years that the age of onset of the affection varies considerably in different families and that there are several modes of inheritance. In macular dystrophy the tendency has been to regard the classical form described by Stargardt which occurs in late childhood or at puberty, as an exclusive chronological and genetic type. That this view as to the age of onset is untenable was shown by Behr, who stressed the occurrence of macular dystrophy later in life. He held that macular dystrophy occurs at the critical periods of development: the first dentition, adolescence, early adult life, the climacteric, and possibly also in old age. Though somewhat schematic, Behr's teaching has the merit of emphasizing that in the macular dystrophies, perhaps even more than in retinitis pigmentosa, there is no one age at which the lesion may occur, and that the classical Stargardt form is merely one of many possible varieties. Likewise, though the recessive type is much the commonest, other forms of inheritance do occur — both regular and irregular dominance and sex-linkage. Furthermore the mottled or pigmentary reaction in the typical macular dystrophies are not the only reactions possible, any



a

Chart. 7. Retinitis pigmentosa. *a*) Recessive inheritance (After E. Nettleship, 1908. Royal Ophthal. Hosp. Rep., 17. 1). *b*) Dominant inheritance (After E. Nettleship. Ibid.). *c*) Recessive sex-linked inheritance (After C. H. Usher, 1935. Trans. Ophthal. Soc. U. K., 55, 164). *d*) Intermediate sex-linked inheritance (After H. F. Falls and C. W. Cotterman, 1948. A.M.A. Arch. Ophthal., 40, 685).

b



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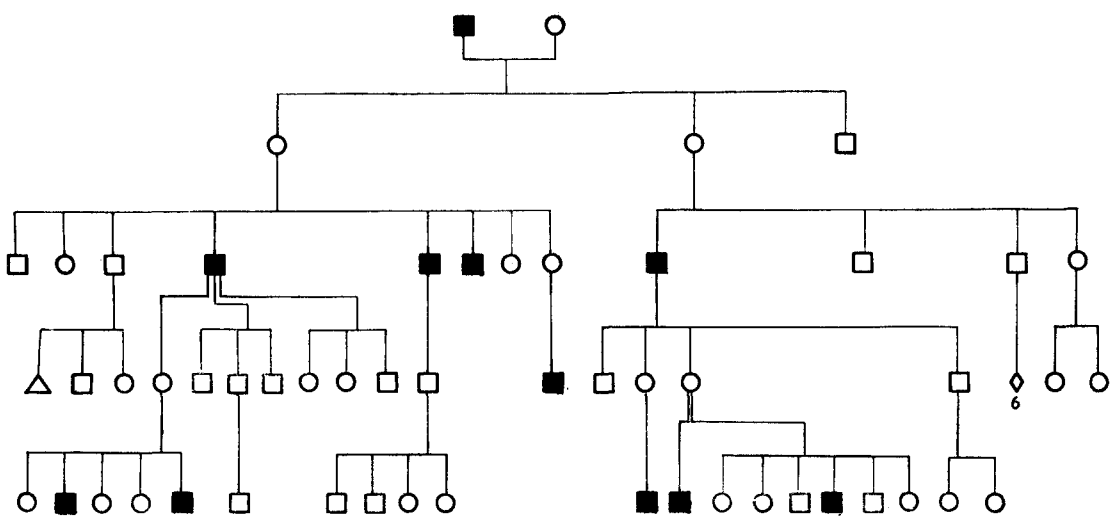

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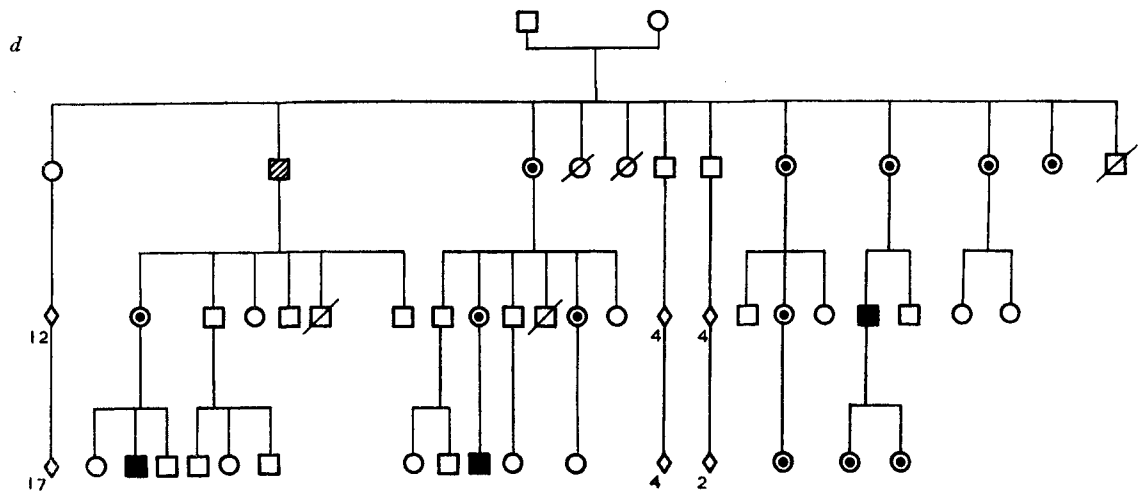

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more than bone corpuscle pigment reaction is the only possible reaction in the retinal abiotrophies. In the macular dystrophies exudative reactions and gross pigmentary changes may replace the more commonly seen lesions (Sorsby, 1940). What is uncertain is whether these morphological variations constitute distinct entities.

Retina

The retinitis pigmentosa group

In view of the great diversity in clinical course and of the modes of inheritance seen with what passes ophthalmoscopically as retinitis pigmentosa, it is necessary to differentiate clear-cut clinical entities.

Four, and possibly six, modes of inheritance of retinitis pigmentosa without generalized associations are recognized. The relative frequency of these different types and the clinical differences between them are known only in broad outline.

Genetic varieties

Recessive. Published pedigrees of retinitis pigmentosa tend to emphasize the exceptional families in which large numbers are affected and the affection is transmitted over several generations. There is, however, no doubt that the relatively infrequently recorded pedigrees of recessive inheritance stand for the bulk of the cases. In a consecutive series of 41 pedigrees of retinitis pigmentosa, Usher found that all but one were recessive. Chart 7*a* illustrates a typical pedigree.

Dominant. The very large number of pedigrees published tends to give an exaggerated importance to the frequency of this mode of inheritance. In all the published pedigrees a striking feature has been the regular mode of inheritance without any skipping of a generation (Chart 7*b*).

Sex-linked recessive. Relatively few pedigrees are available. Chart 7*c* illustrates the typical mode of inheritance. Available evidence would seem to suggest that retinitis pigmentosa with this mode of inheritance is a particularly severe affection. It would also seem that in some families the female heterozygotes are occasionally affected.

Intermediate sex-linked. Falls and Cotterman have drawn attention to this variety of retinitis pigmentosa (Chart 7*d*). As in choroideremia, female heterozygotes can be recognized by ophthalmoscopic changes of no pathological importance. There is a characteristic highly glistening retinal reflex, somewhat reminiscent of the tapetal reflex of animals. Fig. 8 illustrates two such retinal reflexes. The exact significance of this heterozygous manifestation has still to be assessed. A marked tapetal reflex has been observed in a girl who subsequently showed typical retinitis pigmentosa.

Apart from these four modes of inheritance there are two further possibilities suggested by Haldane: recessive and dominant partial sex-linkage (Chart 8 etc.)

Chart 8 supports a reading of dominant partial sex-linkage if cross-over is assumed; the evidence for recessive partial sex-linkage is even less definite.

Ocular associations of retinitis pigmentosa

Glaucoma. The frequency of glaucoma as an association of retinitis pigmentosa has probably been overrated. There is evidence that such glaucoma is genetically determined and not merely incidental (Chart 9*a*).

Cataract. The general assumption that cataract is a secondary manifestation in retinitis pigmentosa is probably not valid. It is possible that cataract is a frequent

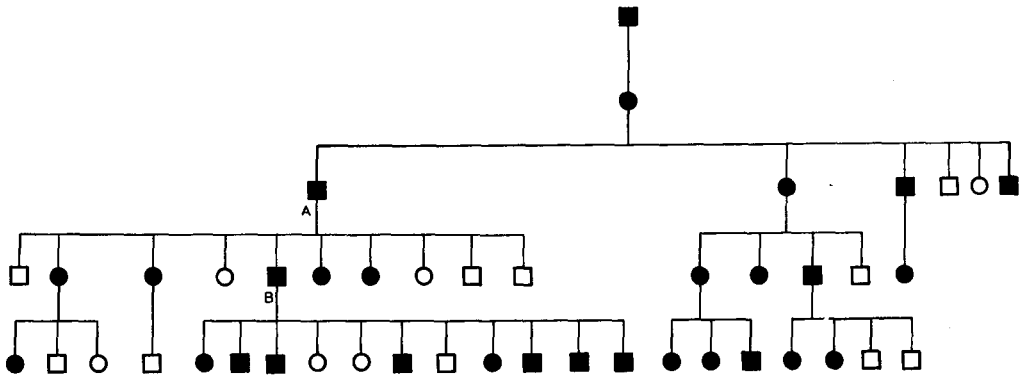


Chart 8. Retinitis pigmentosa. Presumed dominant partial sex-linkage. On the assumption of dominant partial sex-linkage the affected man in the first generation carried the dominant gene on his X chromosome and can have only affected daughters. Such daughters in turn can contribute their abnormal X chromosomes to either sons or daughters. The man marked A in the third generation would again transmit it to all his daughters and to none of his sons. Actually two of his daughters are unaffected, and one son is affected. This can be explained on three cross-overs occurring in this generation. The affected son B in the fourth generation now carries the pathogenic gene on his Y chromosome and would therefore transmit the affection to his sons only. Actually one of his sons is normal and two of his daughters are affected. This, too, would have occurred as the result of cross-over (After S. Snell, Trans. Ophthal. Soc. U. K., 1903, 23, 68. From J. B. S. Haldane. New Paths in Genetics, 1940. London: Allen & Unwin)

and perhaps a constant association of dominant retinitis pigmentosa. Chart 9*b* shows a pedigree of fully developed cataract in dominant retinitis pigmentosa over three generations. In most individuals with dominant retinitis pigmentosa lens changes appear to develop early and to progress fairly rapidly, irrespective of the severity of the fundus lesion.

Cataract would appear to be less common in recessive retinitis pigmentosa. It is, however, possible that there is a variety of recessive retinitis pigmentosa in which cataract is a constant association. Chart 9*c* illustrates such a pedigree.

It would therefore appear that whilst at least four different genes are responsible for the picture of retinitis pigmentosa in different families, there may be as many as

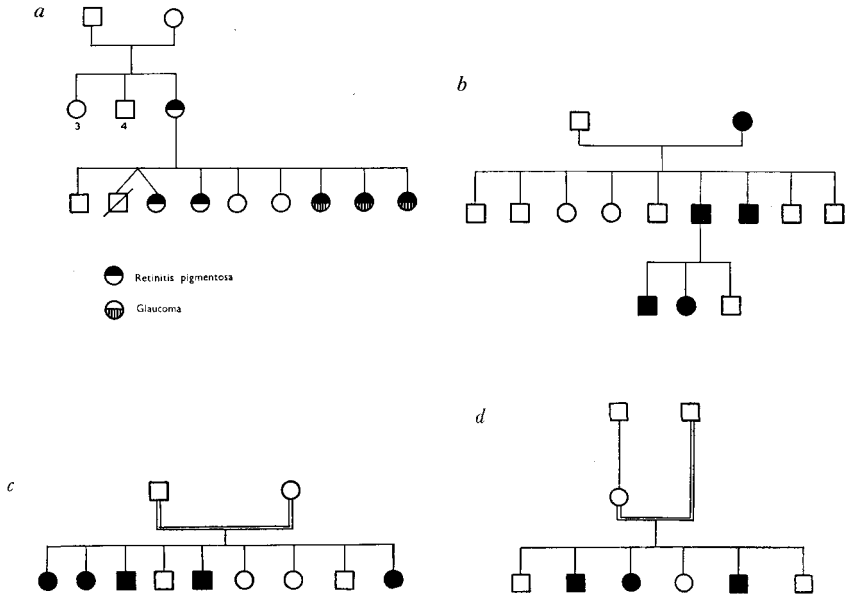


Chart 9. Ocular associations of retinitis pigmentosa. *a*) Retinitis pigmentosa associated with glaucoma. (After A. A. Bradburne, 1916. Ophthal. Rev. 35, 65). *b*) Retinitis pigmentosa with cataract: dominant inheritance (Personal observation). *c*) Retinitis pigmentosa with cataract: recessive inheritance (Personal observation). *d*) Retinitis pigmentosa with macular dystrophy. Pedigree suggestive of recessive inheritance (After A. Sorsby, 1941. Brit. J. Ophthal. 25, 524)

seven and possibly eight distinct forms of retinitis pigmentosa. Intensive combined clinical and genetic studies are necessary for the elucidation of these problems. It is not unlikely that such ill-defined entities as 'atypical retinitis pigmentosa' and 'retinitis punctata albescens' will become more intelligible in the light of such studies.

Ophthalmoplegia. There are case records of external ophthalmoplegia with or without ptosis associated with 'atypical retinitis pigmentosa'. Occasionally present at birth, the onset is most frequently at about puberty and the fundus lesion may be a macular dystrophy or 'atypical retinitis pigmentosa' or both in combination. Nystagmus is present in the congenital cases. The affection has been seen in sibs, but the exact genetic status is uncertain. The association of elements of bulbar palsy with retinal changes recalls the retinal changes seen in the hereditary spino-cerebellar ataxias.

Unusual forms of retinitis pigmentosa

Retinitis pigmentosa with macular dystrophy. The mode of inheritance of this affection is not known. Clinically it is sharply delineated from uncomplicated retinitis pig-

mentosa by the fact that central vision suffers early, with a consequent early total blindness. Chart 9*d* shows a pedigree that suggests recessive inheritance.

Unilateral retinitis pigmentosa. There is nothing to suggest that the rare cases of unilateral retinitis pigmentosa represent a partial manifestation of the hereditary forms of retinitis pigmentosa. The available literature reveals neither an excessive incidence of consanguinity amongst the parents of such individuals, nor any definite family history of the affection. Some of the cases are probably of environmental origin — the consequence of mechanical or chemical injury. Other may represent a somatic mutation.

The macular dystrophies

The classical form of macular dystrophy was described by Stargardt in a series of papers in 1909-17. It was Stargardt's merit that he isolated these purely retinal lesions from the juvenile forms of cerebro-macular degeneration that had been recognized previously. At first regarded as *formes frustes* of the more serious neurological disorders (the Batten-Mayou or the Vogt-Spielmeyer disease), it soon became established that this was an independent disorder with clear-cut features.

As already noted following the isolation of macular dystrophy as a distinct entity, attempts were made to establish different types on the basis of age at onset, and by distinguishing exudative reactions from pigmentary changes. Whilst helpful, these classifications have proved of less value than differentiation by genetic behaviour. At least two and possibly three genetic forms have to be considered.

1) *Recessive macular dystrophy (Stargardt's disease)*

The original studies by Stargardt contain family records that would not now be admitted, either because the lesions extended beyond the macula, or showed symptoms different from those he recorded in his major cases. It is best to confine the name of Stargardt's disease to the recessive type (Chart 10*a* and *b*) occurring in late childhood at puberty.

Clinical features. This affection is characterised by a sudden disturbance in central visual acuity, often declining to 6/36 or 6/60 within a few weeks, and either remaining at this level or possibly showing a slight improvement. Ophthalmoscopically there may be no lesion when vision has already declined, so that retrobulbar neuritis may be mistakenly diagnosed, but before long loss of foveal reflex and fine pigmentary changes become established at the macula (Fig. 9). There is little or no extension away from the central area. In longstanding cases temporal pallor of the optic disc may become a feature. There are no substantial anomalies in colour vision.

2) *Dominant macular dystrophy*

In the literature on macular dystrophy a number of records of dominant inheritance are available. Sorsby and Davey (1955) have shown that these dominant cases,

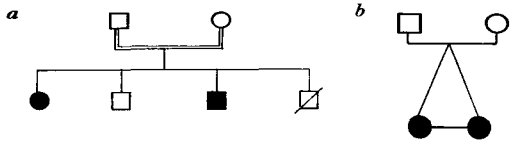
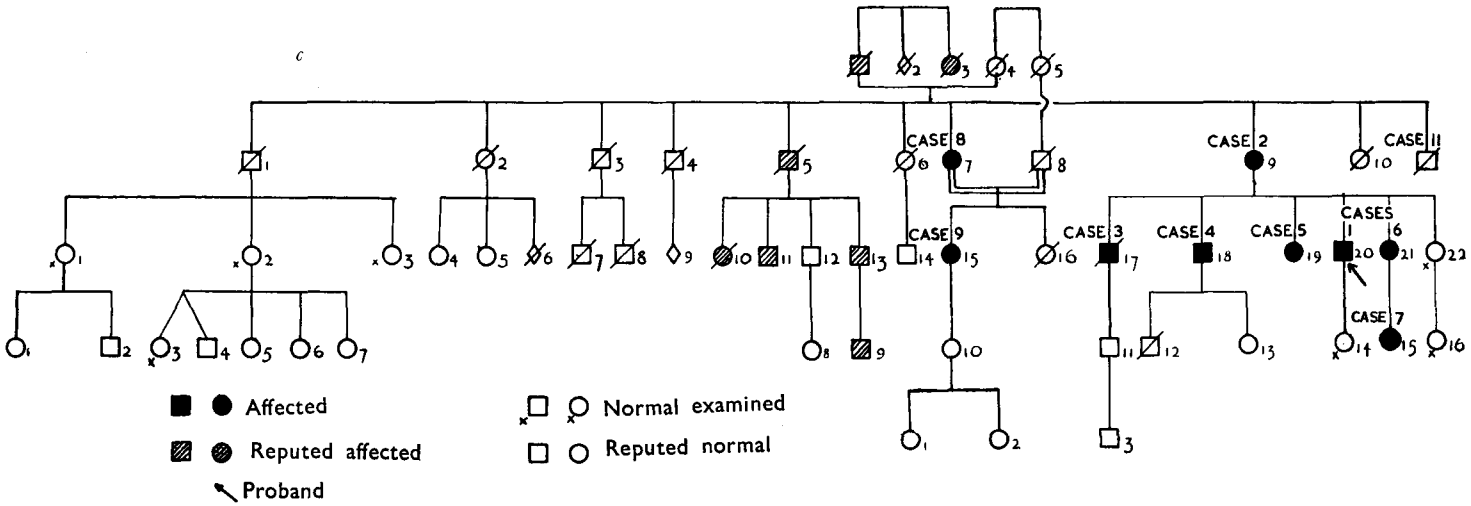
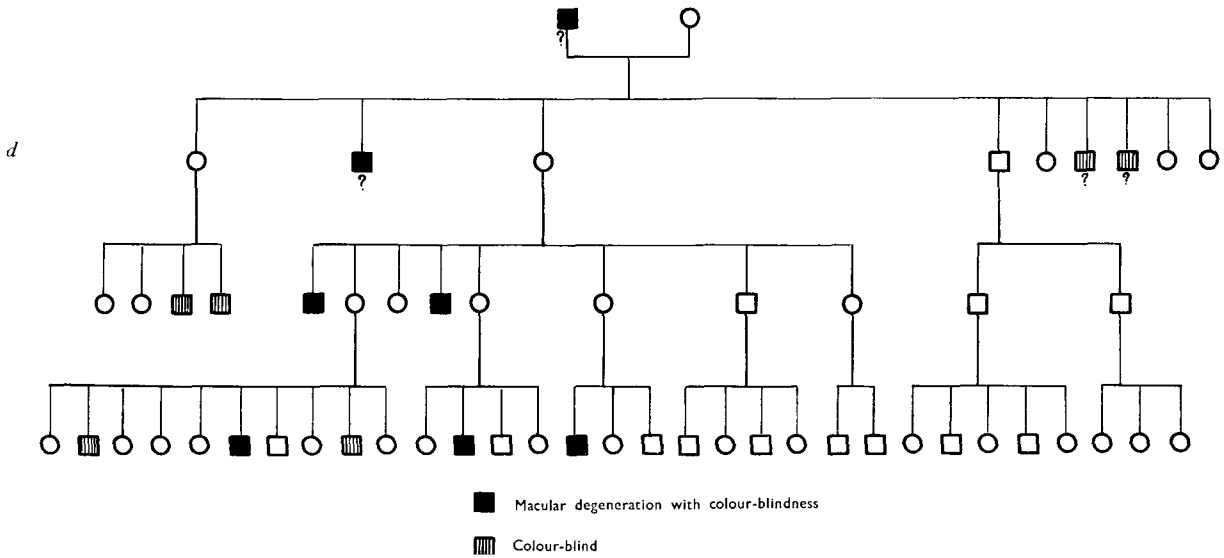


Chart 10. The macular dystrophies. *a*) Pedigree showing the juvenile recessive type. (Stargardt's disease. After H. Neame, 1935. Proc. R. Soc. Med., 28, 526, and personal communication). *b*) Pedigree showing the occurrence of Stargardt's disease, in a uniovular twin (Fig. 9 illustrates the appearances observed ophthalmoscopically. Personal observation). *c*) Pedigree of a family with dominant macular dystrophy (After A. Sorsby and J. B. Davey, 1955. Brit. J. Ophthal. 39, 385). *d*) Pedigree showing recessive sex-linkage (After K. T. A. Halbertsma, 1928. Klin. Mbl. Augenheilk., 80, 794)





though ophthalmoscopically similar to Stargardt's disease, constitute a distinct entity with characteristic features of their own (Chart 10*c*).

Clinical features. The macular lesion is often present for years without any visual symptoms, except for crude anomalies of colour vision, markedly different from the usual red-green defect. Though visual acuity may occasionally decline in childhood, it is often not till adult life or early middle age that symptoms become troublesome. The affection does not set in acutely but takes a slowly progressive course; the end result over years is vision of the order of 6/60. In the elderly, the lesion has sometimes progressed to such an extent that it becomes indistinguishable from 'senile macular degeneration' (Fig. 10).

3) *Sex-linked macular dystrophy*

The possibility of a sex-linked form of macular dystrophy is suggested by Chart 10*d* which records a family with typical macular lesions possibly associated with colour anomalies.

* * *

These macular lesions are all pigmentary in type. Exudative reactions do, however, occur, but are rare; of the two families reported one showed dominant and the other recessive inheritance (Sorsby, 1940). Classification by age is of significance in that in some families recessive macular lesions set in an adult life and do not always run a severe course. Many and perhaps most of the macular dystrophies in middle-age are probably dominant, and often clinically silent for years. There is room for a clearer appreciation of these unusual morphological and chronological forms of macular dystrophy.

Choroid

Choroideremia

Historical. As the name implies, the affection when it was first recognized was regarded as a congenital anomaly due to absence of the choroidal vessels — somewhat parallel to the non-pigmented coloboma of the macula. That the affection was, however, progressive in character, became evident as cases accumulated and less extreme aspects of the disorder were recognized as part of an evolutionary course. The presence of nightblindness as a cardinal sign of the affection and the pigmentary disturbance seen during the course of development, before the ultimate stage of atrophy of the choroidal vessels, led to the assumption that choroideremia was related to retinitis pigmentosa — a reading supported by the fact that at the end stage there was narrowing of the retinal arteries. Further confusion between choroideremia and retinitis pigmentosa came from descriptions of 'atypical retinitis pigmentosa' in some members of families with choroideremia.

These difficulties have now been resolved, and the status of choroideremia as an

independent affection, abiotrophic in type, is now unquestioned. Choroideremia shares with retinitis pigmentosa the symptom of nightblindness and retention of central vision until towards the end; otherwise the two affections have very little in common. The mode of inheritance of choroideremia has been shown to be sex-linked, and the 'atypical retinitis pigmentosa' observed in families with choroideremia has been recognized as instances of the carrier state in women.

Clinical features. The mildest changes of choroideremia have been observed in boys in the first years of life when the fundus shows fine granular changes, indistinguishable from the changes seen in carrier women. The progressive nature of these changes is illustrated in Fig. 11, whilst the essentially stationary character of the carrier state is shown in Fig. 12. Though the affection in males is relentlessly progressive, the severity is not directly related to age: blindness may supervene as early as the twenties, or not until as late as the sixties. There is nothing to suggest that the changes seen in the carrier state are progressive: the mild carrier state has been observed in elderly women, whilst young girls have shown marked changes. That choroideremia should give the symptoms of retinitis pigmentosa and ultimately the narrowing of arteries and the optic atrophy reminiscent of retinitis pigmentosa is not unexpected in view of the fact that there is a slow cutting off of the blood supply to the retina, so that inevitably there is a slowly developing death of the retina with attendant progressive loss of function and structure.

Differential diagnosis. At the end stage the picture of choroideremia is unmistakable: the white glistening sclerotic dominates the fundus background, broken only here and there by tufts of choroidal vessels and mild pigment changes, whilst the disc is atrophic and the retinal vessels narrow. Choroidal vessels persist longest at the central area. Before the end stages, the diagnosis presents considerable difficulty, as narrowed or obliterated choroidal vessels are seen against the fundus background and the diagnosis of choroidal sclerosis is feasible. At an earlier stage still the mottled reaction of the fundus, particularly towards the periphery, is, as already mentioned, indistinguishable from the marked carrier state and in mild cases may well be regarded as a physiological variation, and in more severe cases as a variant of 'pepper and salt' fundus.

In the carrier state the peripheral pigmentary mottling is highly suggestive and may be mistaken for a physiological variation, but is unlikely to be mistaken for the characteristic tapetal reflex seen in the carrier state of retinitis pigmentosa.

Morbid histology. The fullest account has come from a study of 4 eyes from the families reported by the McCullochs (1948). The choroidal vessels were either sclerosed or absent, and the outer layers of the retina extensively degenerate or totally lacking. The retinal changes were proportionate to the choroidal changes throughout; where the choroid was relatively intact the retina appearad to be least involved. The choroidal changes were regarded as the primary lesion.

Heredity. As choroideremia is inherited in an intermediate sex-linked manner (Chart 11), it is possible to recognize the carrier women readily by the characteristic fundus appearances. It should, however, be noted that these appearances may be minimal and easily missed.

Choroidal sclerosis

Sclerosis of the choroidal vessels is an aspect of many fundus disturbances. Involutionary changes of the athero-sclerosis type in the choroidal vessels are histologically a normal feature of senescence, and are apparently present as early as the age of 40. Pathological obliteration of the choroidal vessels is suggested when the choroidal vessels stand out ophthalmoscopically as white streaks against the fundus background, but histologically in some such cases the choroidal vessels have been found patent and the sheathing along the vessels the result of connective tissue proliferation in between the vessels. Appearances suggestive of choroidal sclerosis are also seen in generalized fundus dystrophy and, as already noted, during the evolution of choroideremia. In the literature on retinitis pigmentosa there is the repeated suggestion that there are two types of this affection, a choroidal or mesodermal type and a retinal or ectodermal type — the choroidal type being characterized by obvious choroidal sclerosis not generally seen in the retinal type. Likewise, in the normal fundus it is not easy to distinguish *fundus tigré* with its normal choroidal circulation from early choroidal sclerosis producing an ophthalmoscopically similar patterning. Nonetheless there is apparently a genuine counterpart to choroideremia in so far that there is a primary choroidal disturbance shown not by the disappearance of the choroidal vessels as in choroideremia, but by their conversion into obliterated white cords. Choroidal sclerosis as a clinical entity has been well established for years, but its genetic character has been recognized only fairly recently.

Three hereditary forms of choroidal sclerosis can be distinguished:

1) *Central choroidal sclerosis*

The characteristic appearances of a sharply delineated circular or transversely oval patch of choroidal sclerosis was known to Liebreich as early as 1862, and was described by Nettleship in 1884 under the designation of central senile areolar choroidal atrophy. Fig. 13 shows the affection as seen in two brothers at about the age of 60, whilst Fig. 14 shows a wider range of appearances, including the earliest stages, over a wider range of ages. It is clear that the designation 'senile' is inapplicable, and that the earliest changes may occur by the age of 20 or before, and take the form of white dots over the central area. A number of families studied are now available and whilst recessive inheritance appears to be the rule (Chart 12*a*), two families are known in which it occurred as a dominant disorder (Chart 12*b*).

Whilst the affected area is generally sharply delineated from the rest of the fundus, individual cases do show some ill-defined choroidal sclerosis extending beyond the central area; this, however, is exceptional.

Subjective symptoms. There is no nightblindness and the visual symptoms follow on the slow shutting off of the blood supply to the central area, so that central vision declines and at the height of the affection is reduced to counting fingers; the peripheral vision remains intact.

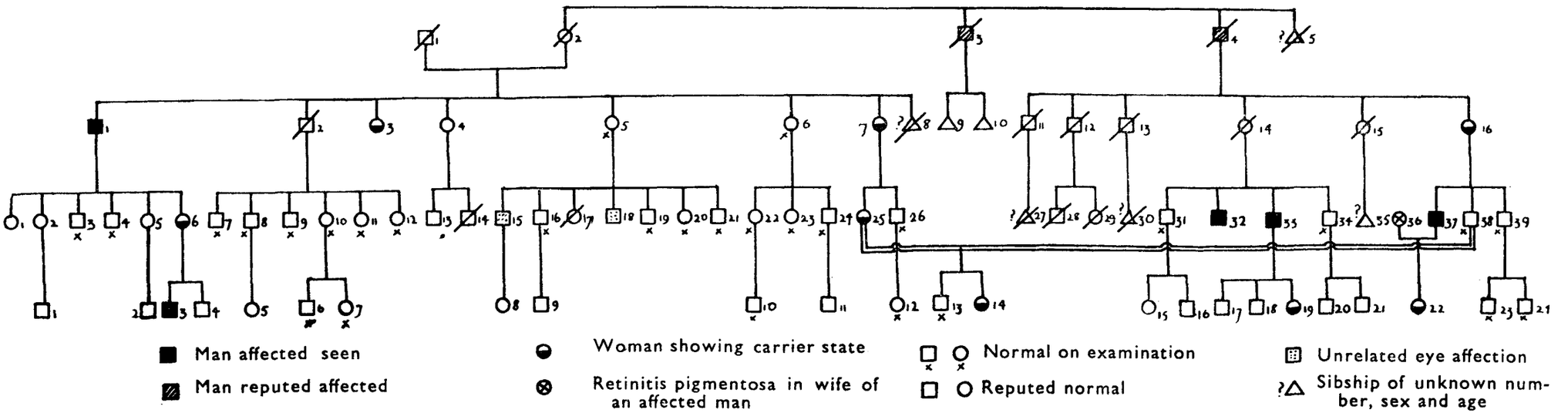
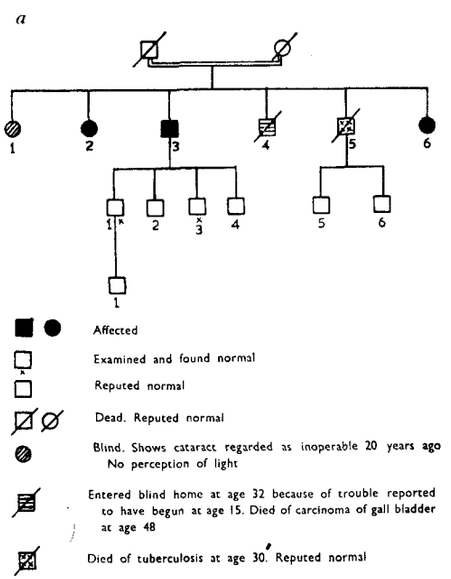


Chart 11. Choroideremia. Pedigree showing intermediate sex-linked inheritance (After A. Sorsby, A. Franceschetti, R. Joseph and J. B. Davey, 1952. Brit. J. Ophthal. 36, 547)



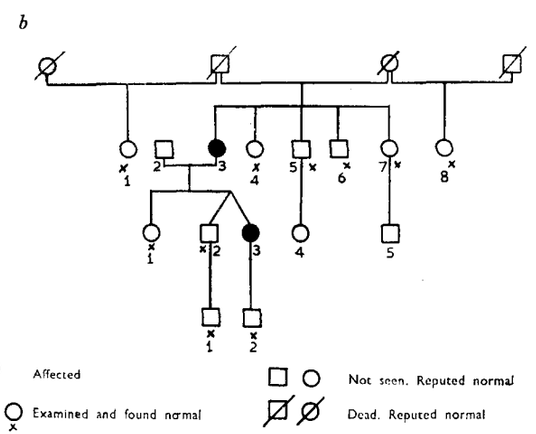
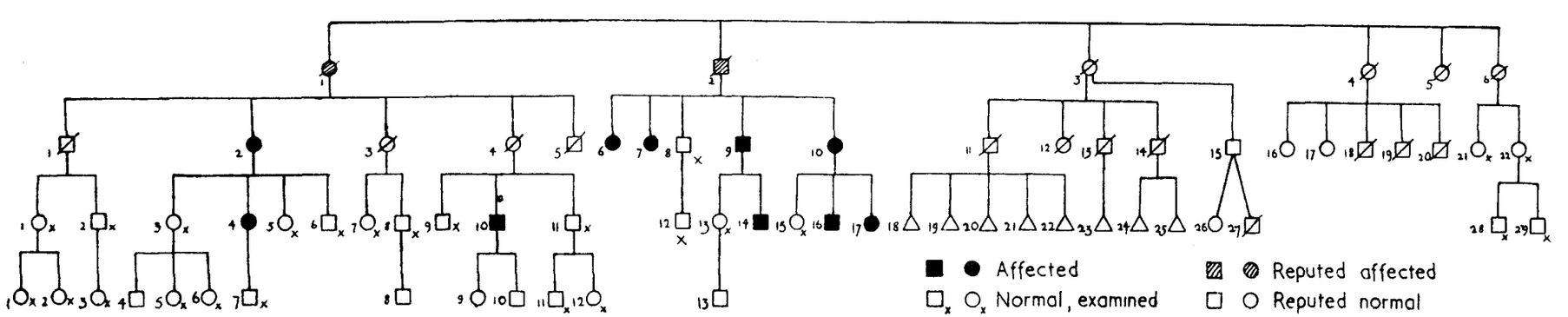


Chart 12. Central choroidal sclerosis. *a*) Recessive inheritance (After A. Sorsby and R. P. Crick, 1953. Brit. J. Ophthal. 37, 129). *b*) Dominant inheritance (After A. Sorsby and R. P. Crick, ibid.)

Chart 13. Generalized choroidal sclerosis. Dominant inheritance (After A. Sorsby and J. B. Davey, 1955. Brit. J. Ophthal. 39, 257)



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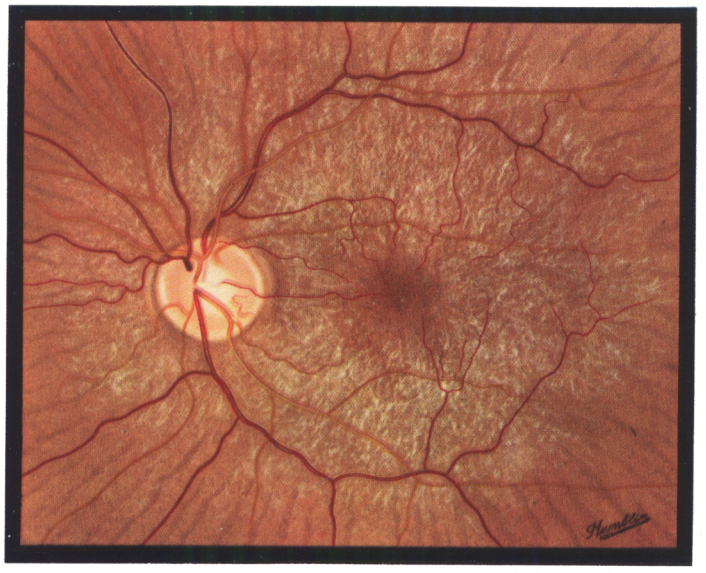

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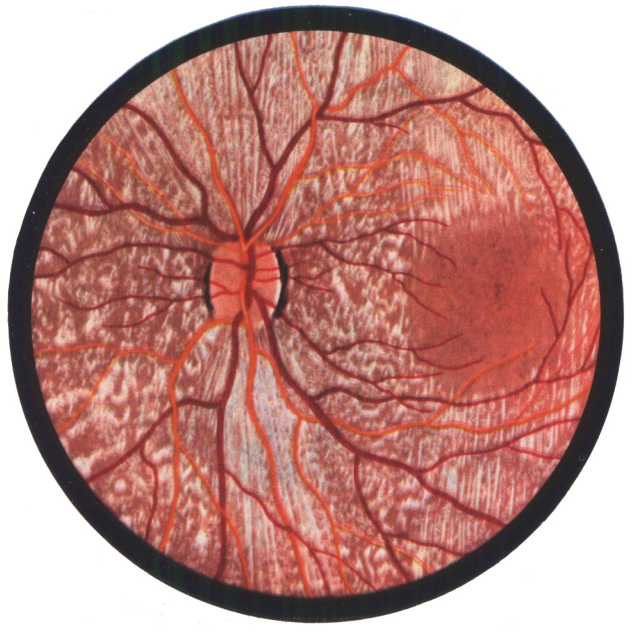
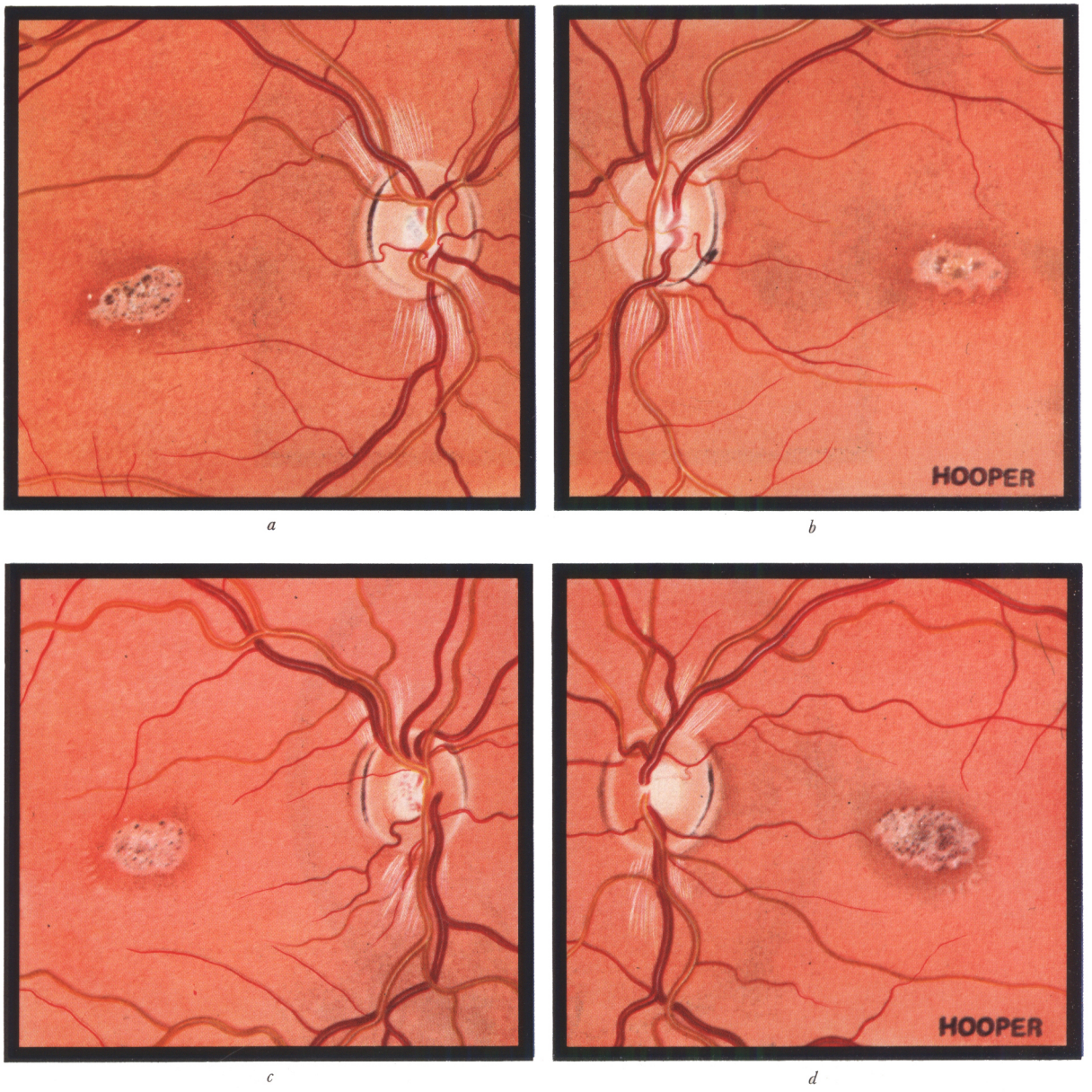


b

Fig. 8. Tapetal reflex in the female carriers in sex-linked retinitis pigmentosa.
a) In a personally observed family (After Sorsby A., Genetics in Ophthalmology. London: Butterworth., 1951).
b) In a case recorded in 1902 as a physiological anomaly in a girl whose family history shows her father to have suffered from retinitis pigmentosa (After A. W., Frost, 1902. Trans. Ophthal. Soc. U. K., 22, 208)



a *b*

c *d*

Fig. 9. Macular dystrophy. The recessive type (Stargardt's disease) in twin girls aged 11 (Personal observation)

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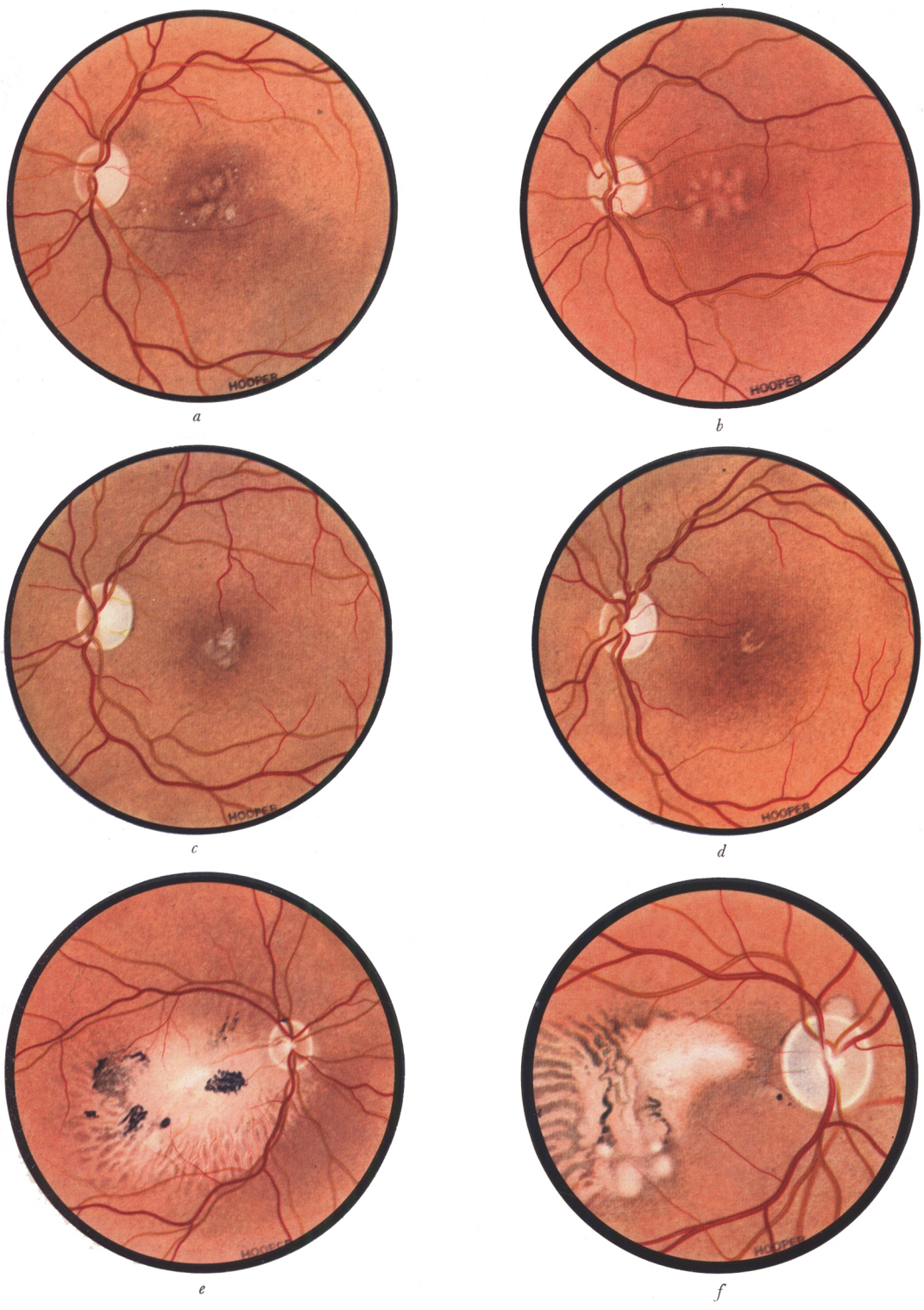

Fig. 10. Macular dystrophy. The dominant type. Appearances in a family over three generations.
a) A man aged 51. *b*) His mother aged 83. *c*) His sister aged 49. *d*) Her daughter aged 24. *e*) A sister of the woman shown in *b*), aged 86. *f*) Her daughter, aged 61.
In all but the patient shown in *d*) vision was grossly affected; gross colour defects were present in all patients
(After Sorsby A., and Davey J. B., 1955. Brit. J. Ophthal. 39, 385)

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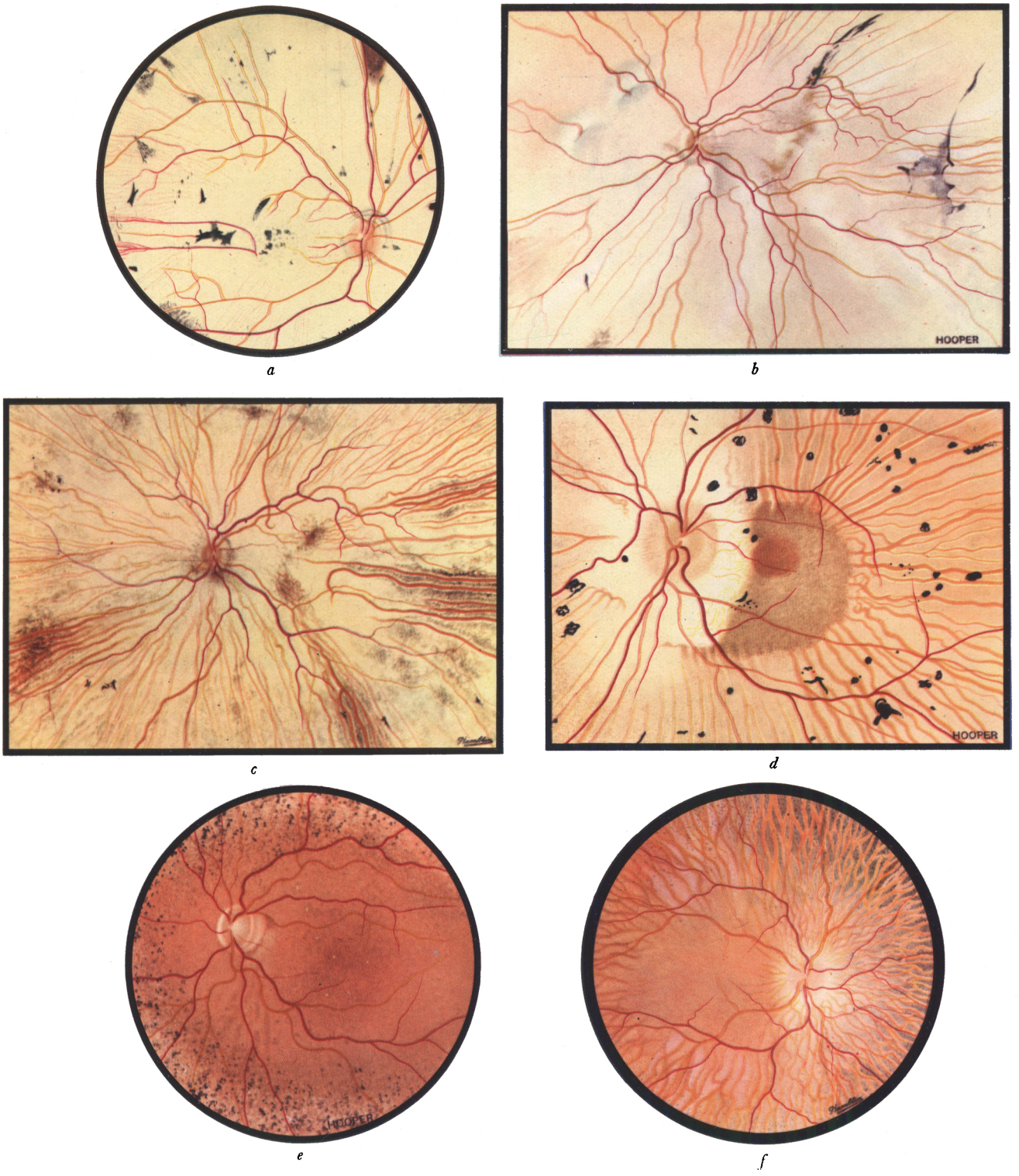

Fig. 11. Choroideremia. Range of appearances in males.
a) Appearances in a man aged 57. *b*) Appearances in a cousin aged 41. *c*) Appearances in the man shown in *b*) 13 years previously. *d*) Appearances in a man (in an unrelated family) aged 35. *e*) Appearances in a youth (in another unrealted family) aged 18. *f*) Appearances in a boy aged 4, a member of a collateral branch of the family illustrated in *a*), *b*) and *c*) (After Sorsby A., Franceschetti A., Joseph R., and Davey J. B., 1952. Brit. J. Ophthal. 36, 547)

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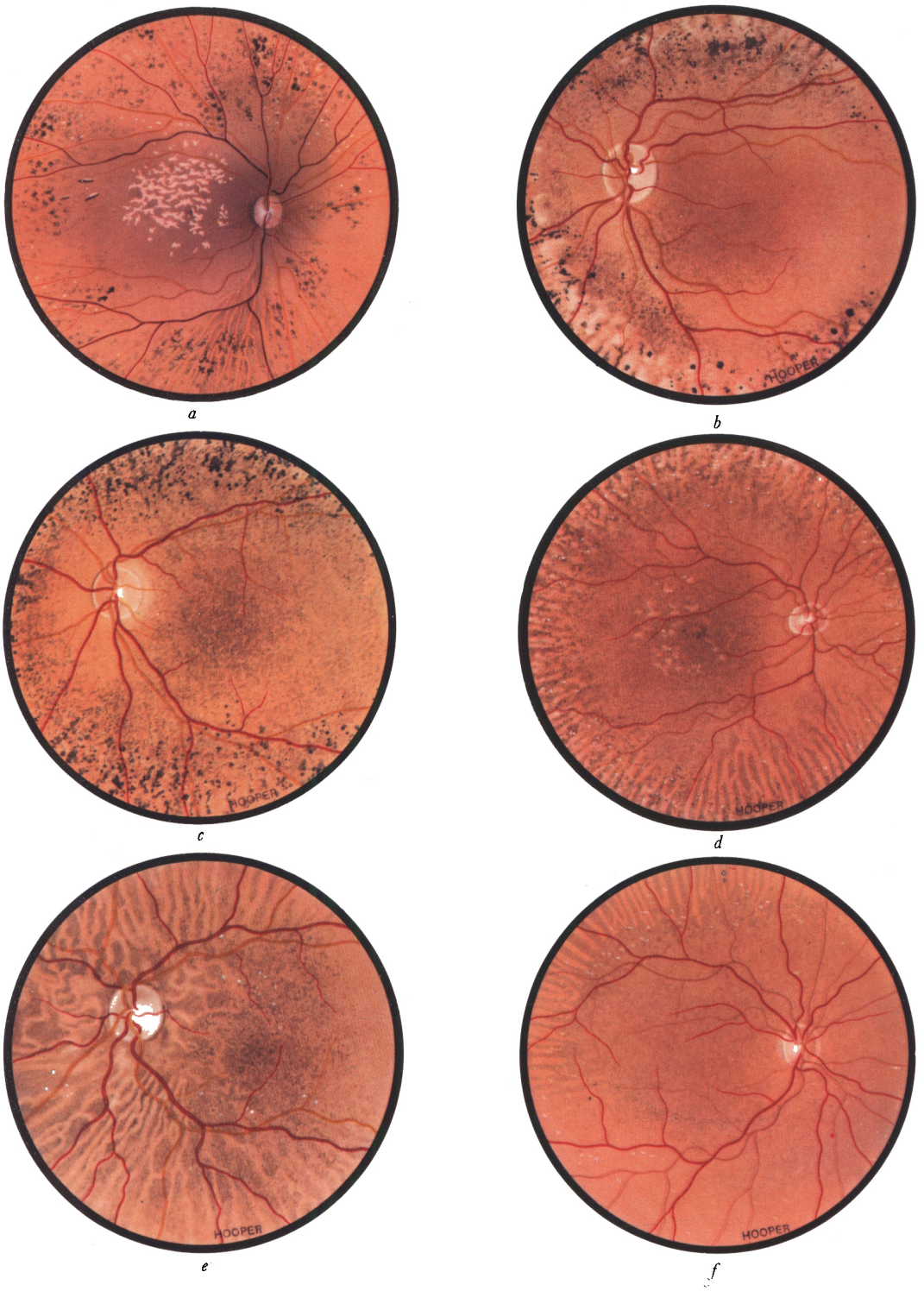

Fig. 12. Choroideremia. Range of appearances in female carriers.

a) Appearances in a woman aged 23, a member of the family depicted in Fig. 11 *a*), *b*), *c*) and *f*). (Vision was unaffected in spite of the central lesion).

b) Appearances in a woman aged 45, the mother of the youth shown in Fig. 11 *e*).

c) Appearances in a girl aged 3, the daughter of the man shown in Fig. 11 *d*).

d) Appearances in a girl aged 14, daughter of the woman shown in *f*).

e) Appearances in a woman aged 65, mother of the man shown in Fig. 11 *b*) and *c*).

f) Appearances in a woman aged 39, mother of the girl shown in *d*) and sister of the woman shown in *b*).

(After Sorsby A., Franceschetti A., Joseph R., and Davey J. B., 1952. Brit. J. Ophthal. 36, 547)

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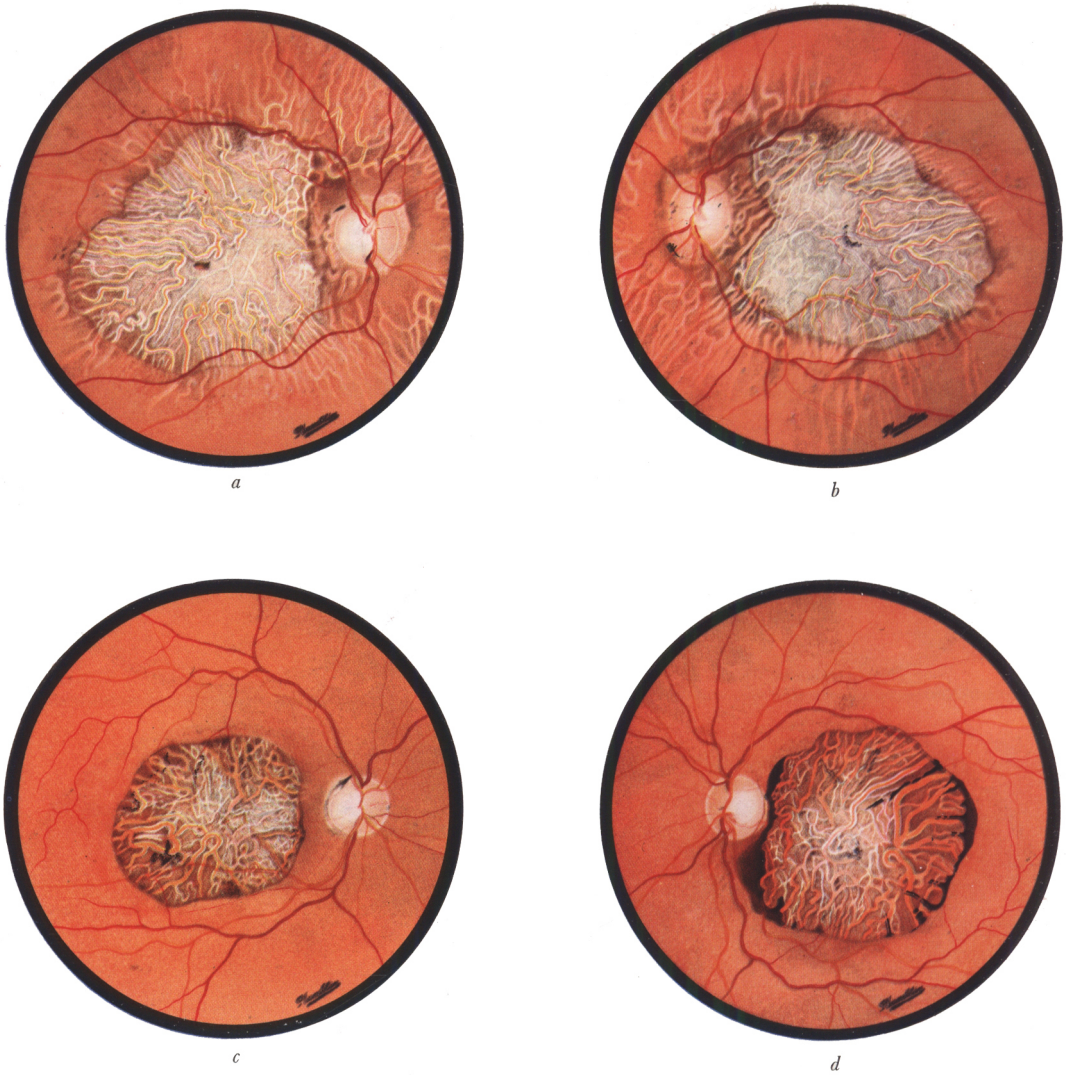

Fig. 13. Central choroidal sclerosis. Appearances in two brothers aged 59 and 63.
a) and *b*) Appearances in the younger brother.
c) and *d*) Appearances in the older brother.
(After Sorsby A., 1939. Brit. J. Ophthal. 23, 433)

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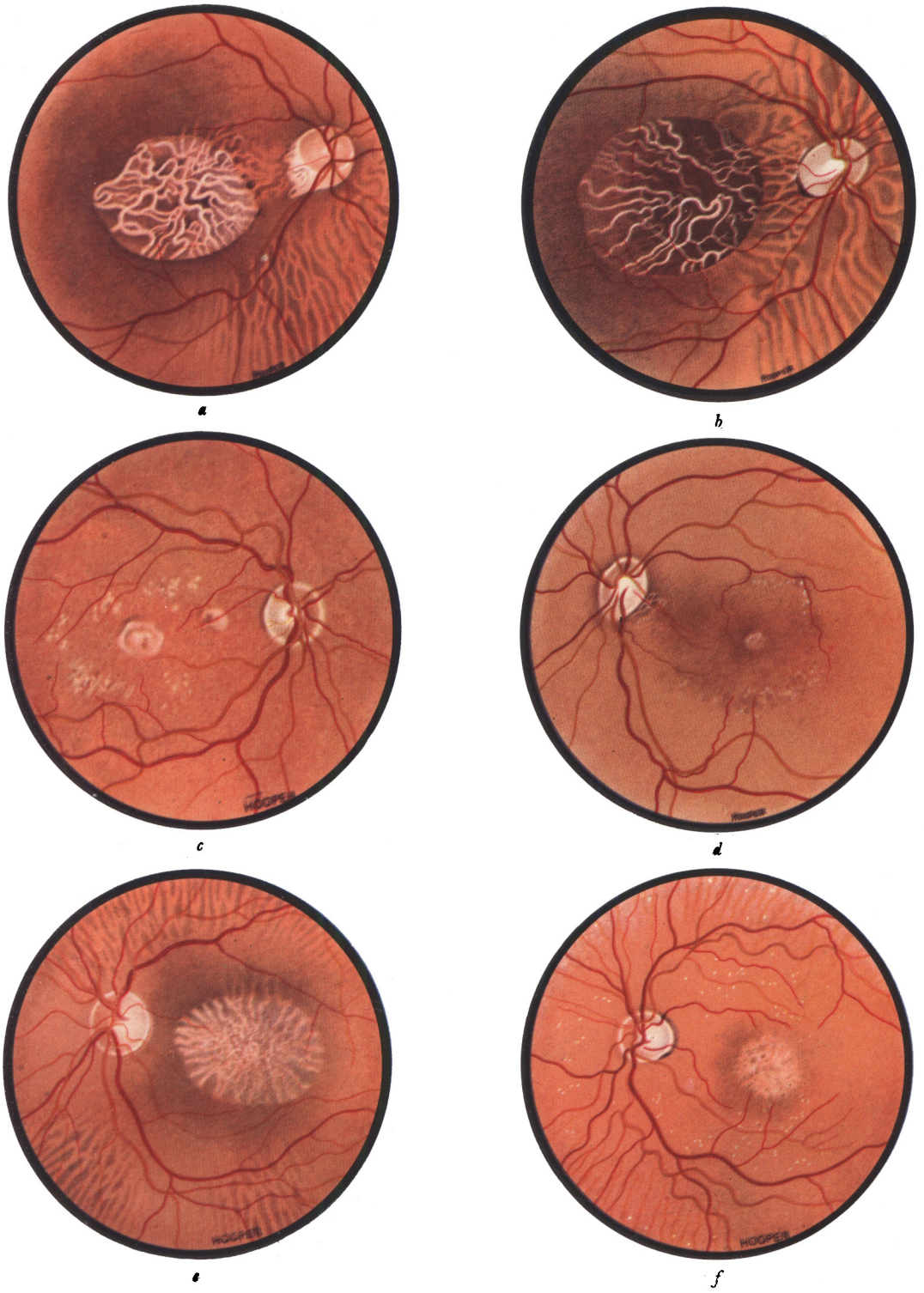

Fig. 14. Central choroidal sclerosis. Appearances in a sibship with the recessive type, and in a mother and daughter with the dominant type.

a)-*d*) Appearances in a woman aged 56, her brother aged 50, and her sisters aged 60 and 54 respectively.

e) and *f*) Appearances in a woman aged 58 and her daughter aged 30 (After Sorsby A., and Crick R. P., 1953. Brit. J. Ophthal. 37, 129)

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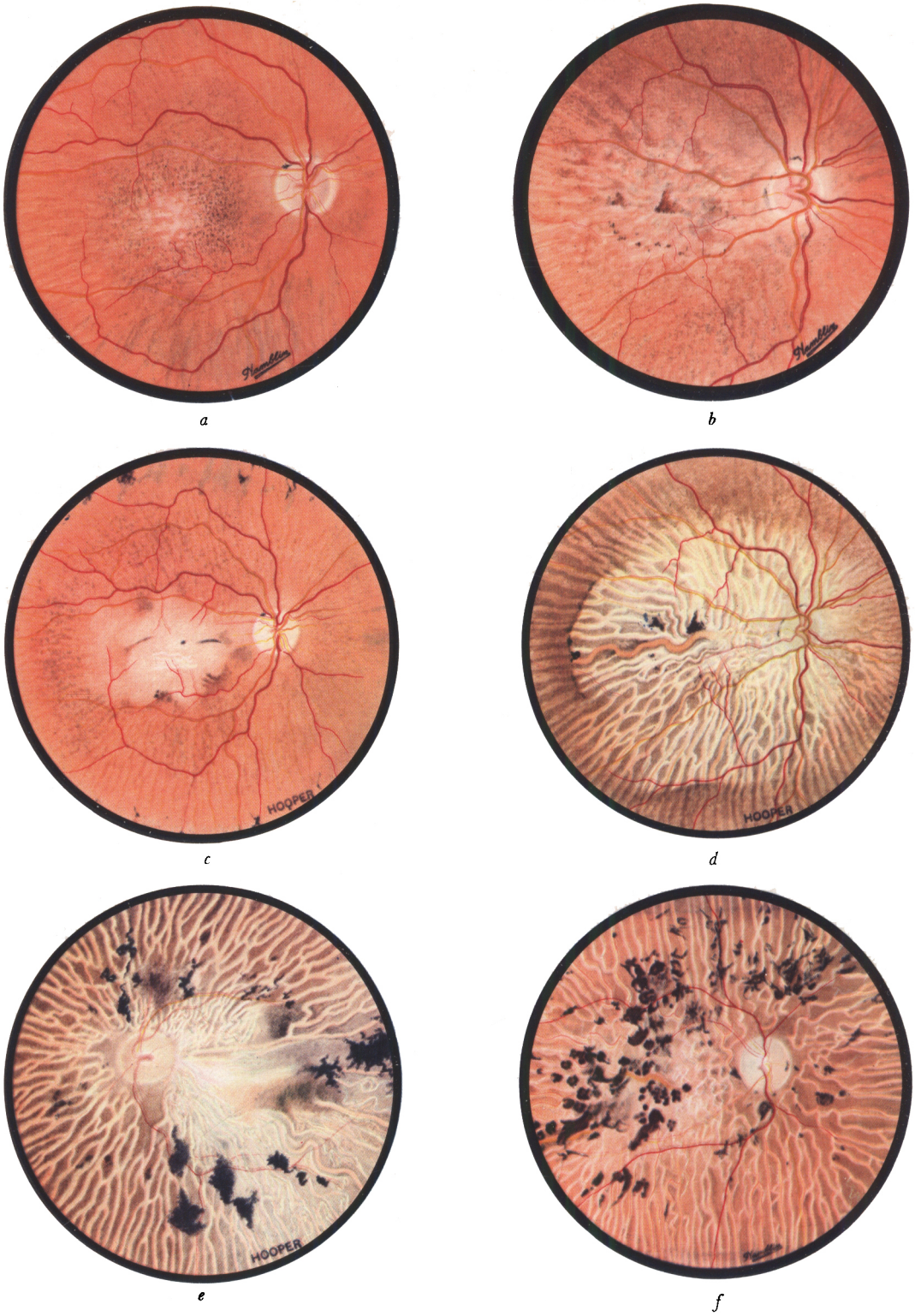

Fig. 15. Generalized choroidal sclerosis. Range of appearances beginning as a macular lesion and extending to widespread atrophy.
a) and *b*) Appearances in two sisters at the age of 43 and 40 respectively.
c) and *d*) Appearances 17 years later.
e) and *f*) The end stage seen in a man aged 75 and his sister aged 61 years — unrelated to the above patients. (After Sorsby A., and Davey J. B., 1955. Brit. J. Ophthal. 39, 257)

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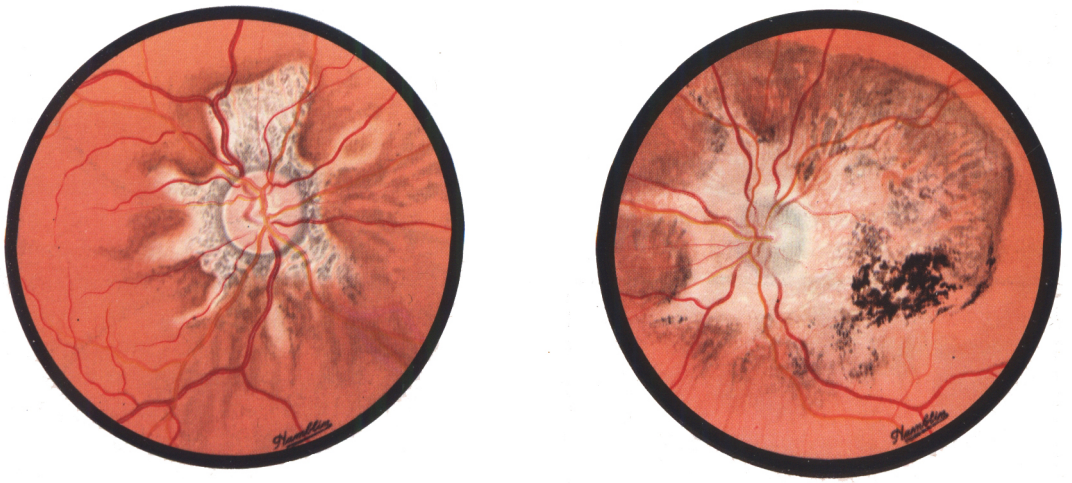

Fig. 16. Peripapillary choroidal sclerosis. Appearances in two sisters (After Sorsby A., 1939. Brit. J. Ophthal. 23, 433)

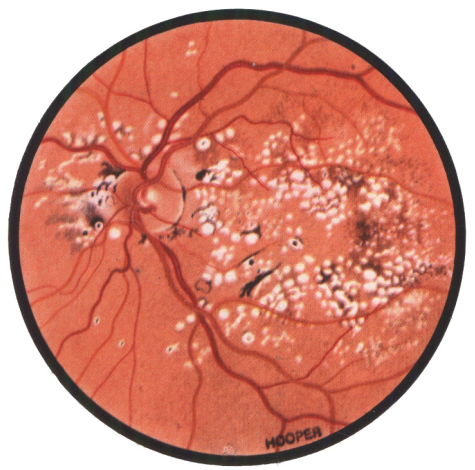

Fig. 18. 'Doyne's choroiditis'. Appearances in a man aged 44 — a member of one of the families originally described by Doyne. Some are affected very mildly

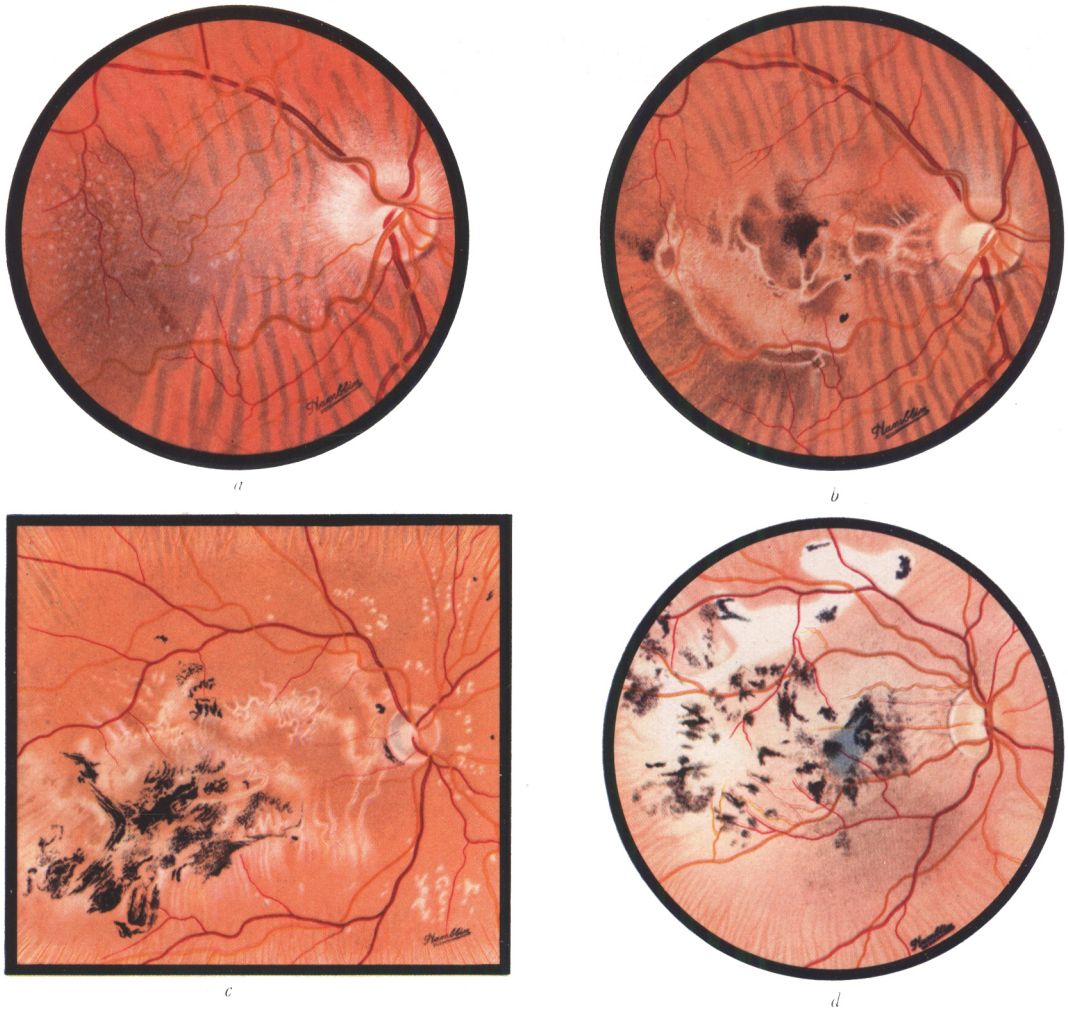

Fig. 17. Generalized dominant fundus dystrophy. Range of ophthalmoscopic appearances as seen in one family.

a) Earliest stage showing neuroretinal oedema, haemorrhages and exudates in a patient aged 41 years.

b) The same eye 22 months later, showing scar formation.

c) Appearances in a cousin of the patient at the age of 68 years; patterned exudates, pigmentary reaction, and early choroidal sclerosis are all evident.

d) Appearances in an uncle at the age of 57 years. There is considerable atrophy.

e) Appearances in an aunt at the age of 77 years. There is extensive atrophy and considerable choroidal sclerosis, and some pigmentary disturbance. There is also a coincidental glaucomatous optic atrophy (After Sorsby A., and Mason M. E. J., 1949. Brit. J. Ophthal. 33, 67)

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Morbid histology. The one study available suggested that the choroidal vessels were not grossly affected but patterned by exudation. It is difficult to fit this with the ophthalmoscopic appearances and clinical course.

2) *Generalized choroidal sclerosis*

This groups is not so well defined as central choroidal sclerosis. The ophthalmoscopic appearances of the choroidal vessels as white streaks is indeed unmistakable, and the distribution of these white streaks all over the fundus justifies the designation of generalized chroidal sclerosis. The earliest stages of this affection — as the earlier stages of central choroidal sclerosis — are represented by white dots over the fundus, with possibly mild pigmentary disturbances; these are indicative of the slow dying of the overlying retina (Fig. 15*a-d*). The difficulty is to know whether these appearances will ultimately lead to the fairly clear-cut picture of conversion of the whole of the choroidal pattern into white streaks (Fig. 15*e* and *f*), or whether the intermediate stages ultimately finish in either the picture of choroideremia or generalized fundus dystrophy — or even retinitis pigmentosa. Family studies are therefore particularly important in the diagnosis of choroidal sclerosis, and further studies are needed on the subjective symptoms, particularly on night-blindness.

Heredity. It is likely that generalized choroidal sclerosis is dominant (Chart 13) a point that helps to distinguish it from retinitis pigmentosa (with its usual recessive course) and from choroideremia with its sex-linkage.

3) *Peripapillary choroidal sclerosis*

In one sibship, two sisters were affected with a marked peripapillary choroidal sclerosis (Fig. 16) reminiscent of *Caput Medusae* of the early ophthalmological literature. Further studies are needed.

Abiotrophies of possibly retinal or possibly choroidal nature

The four affections described in this section are of uncertain pathology. Such histological evidence as is available suggests that generalized fundus dystrophy may follow on changes in the membrane of Bruch, linking it histologically but not clinically nor genetically with disciform degeneration of the macula. The nature of Doyne's choroiditis is also unknown. The one study available suggests that it is due to massive colloid formation, again at the membrane of Bruch. The pathological basis of the so-called senile macular lesions is obscure, though some at least are the result of primary retinal lesions, as are the macular lesions seen in the elderly members of families with dominant macular dystrophy. As for gyrate atrophy, its very existence as a separate entity is in question.

Dominant generalized fundus dystrophy

Historical. The affection was described by Sorsby and Joll Mason in 1949. Few case reports have as yet appeared, but the condition is not uncommon. The intermediate stages show an exceptionally wide range of appearances, presenting considerable difficulties in the diagnosis of individual cases.

Clinical features. The affection commonly begins at about the age of 40 years. The first subjective symptoms are blurring of central vision in one eye followed by the same symptoms in the other eye within a matter of months, or perhaps within a few years. It is not known whether the two eyes may be affected simultaneously. Central vision rapidly declines, but there is no involvement of peripheral vision or

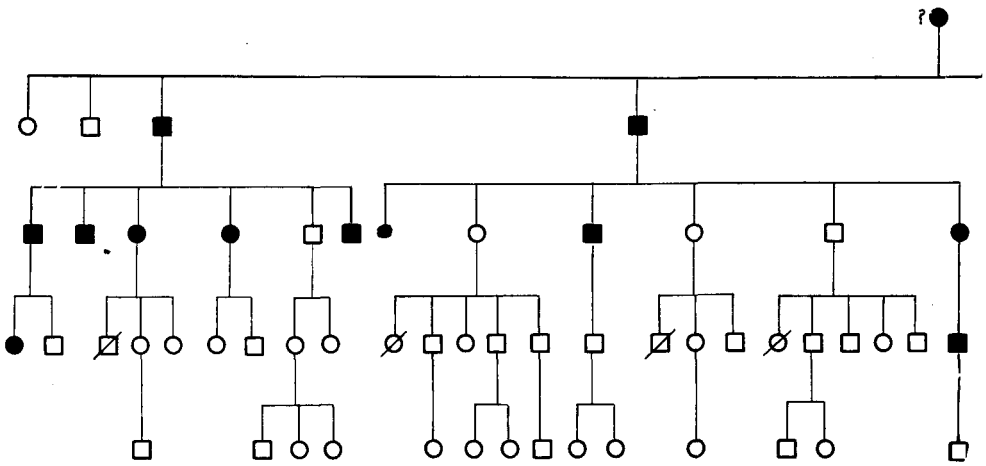

Chart 14. Generalized fundus dystrophy. Pedigree showing dominant inheritance (most of the members of the fourth and fifth generations have not yet reached the age of manifestation of the affection) (After A. Sorsby, and M. E. J. Mason, 1949. Brit. J. Ophthal. 33, 67)

colour vision at this stage. There are no symptoms of night-blindness early on or during the course of the affection.

Objectively the first signs are oedema, haemorrhages, and exudates in the central area (Fig. 17). This progresses to scar formation with a varying amount of pigment proliferation, which may be exceedingly massive. The choroidal vessels become exposed and show some sclerosis. Over the course of years the process extends peripherally, choroidal sclerosis generally becomes more manifest and sometimes dominates the picture. During its spread peripherally, exudates — sometimes patterned — may appear. Occasionally, widespread glistening 'colloid' bodies may be a pointing sign. The end-stage is extensive disappearance of the choroidal vessels exposing the sclerotic covered irregularly by proliferating pigment. The terminal stage produces practically total blindness. The full course of the affection spreads normally

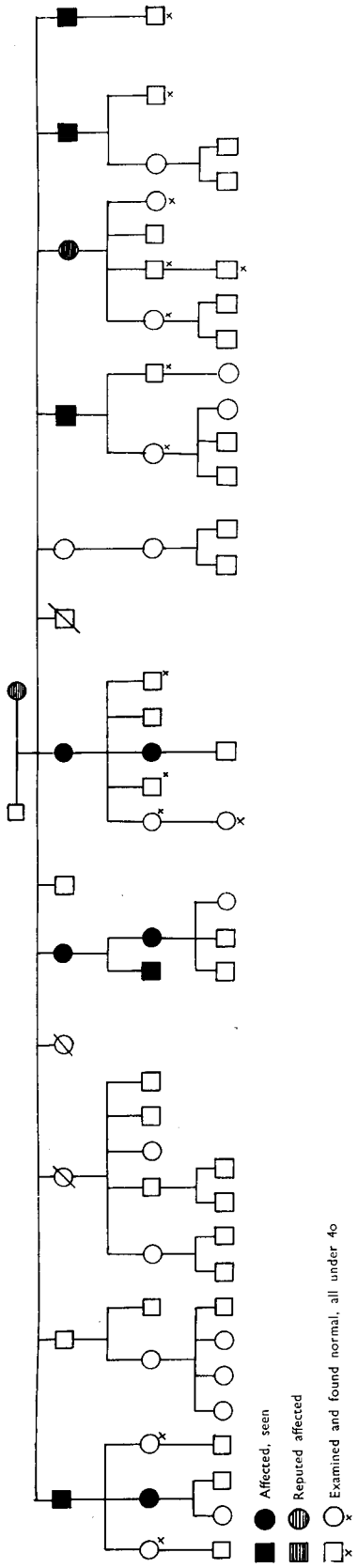

Chart 15. Doyne's 'Choroiditis'. Dominant inheritance (Personal observation, unpublished)

over about 35 years. The process may, however, be milder or more severe in individual cases.

The polymorphism of the fundus reactions is such that any stage of oedematous and inflammatory fundus lesions as well as diffuse choroidal sclerosis can be simulated.

Histology. Ruptures in the membrane of Bruch were the outstanding features in two sisters with this affection. Clinically these cases were not quite conclusive examples of the affection, so that further studies are needed.

Heredity. Genetically the condition is a simple autosomal dominant (Chart 14).

Doyne's 'choroiditis'

This patterned form of central retinal dystrophy (Fig. 18) has these unusual features:

a) The lesion is much more extensive than Stargardt's disease or dominant macular dystrophy, though it never becomes a generalized disorder extending over the whole of the fundus.

b) Instead of pigmentary reaction there are white reactions of the colloid body type, occasionally becoming patterned into the 'honeycomb' described by Doyne. The 'honeycomb' itself is exceptional, but the white patterned lesion is characteristic.

c) At the later stages fine lines of pigment proliferation appear.

The affection is dominant (Chart 15) and has been recorded in Switzerland under the name *Maladie Leventinese*. It is apparently not common, though its frequency may be underestimated owing to the fact that most cases run a mild course and many sufferers are unaware of the existence of their trouble. In only a minority of patients is central vision affected. Commonly, in addition to the macular and paramacular lesion, colloid bodies are also to

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be observed on the nasal edge of the disc. When present they are of considerable diagnostic significance.

Doyne's choroiditis, when it does give trouble, is unlikely to do so before middle-life, though ophthalmoscopic evidence of the affection may be present very much earlier — as early as twenty or before.

'Senile macular degeneration'

It has already been observed that the end-stage of dominant macular dystrophy may simulate so-called senile macular degeneration. It is possible that same cases of macular lesions in the elderly are genetically determined; the evidence is as yet indefinite.

Gyrate Atrophy

It is unlikely that gyrate atrophy is a stage in the development of choroideremia, as has been repeatedly suggested. Though many cases of gyrate atrophy have been followed up, in no case is there a record of choroideremia as the end-result. Ophthalmoscopically, a plexus of blood vessels at the macula is common in choroideremia, but is not seen in gyrate atrophy. Moreover, the two affections have a different mode of inheritance: gyrate atrophy is said to be recessive, choroideremia is clearly sex-linked. High myopia is said to be common in gyrate atrophy.

Differential diagnosis in the dystrophies of the retina and choroid

The retinal dystrophies present considerable diagnostic problems. The differentiation of a macular dystrophy from the retinitis pigmentosa group is simple enough, both ophthalmoscopically and by the symptoms. Difficulties arise when the macular dystrophies have to be distinguished on the one hand from congenital macular lesions simulating macular dystrophies, and on the other hand from extensive retinal and choroidal disturbances which begin as central lesions.

The distinction from the relevant congenital lesions — macular cyst and asymptomatic macular defects — has already been considered.

The distinction between the recessive and the dominant forms of macular dystrophy is obvious from their clinical course. Differentiation from Doyne's choroiditis which is a central lesion generally presents no difficulty, for Doyne's choroiditis has a characteristic ophthalmoscopic appearance, clinical course, and clearcut dominant inheritance. The macular lesion of angioid streaks also presents no difficulty because of the ophthalmoscopic appearances and general associations. Differentiation from central choroidal sclerosis at its early stage is the presence of white dots as the pointing sign of choroidal sclerosis as against the loss of macular lustre and fine pigmentation seen with the macular dystrophies; family studies often help. Generalized fundus

dystrophy, dominantly inherited, usually begins in a stormy manner with haemorrhages and exudates at about the age of 40, and is unlikely to present confusion. The most substantial difficulties are in the ill-defined retinal and choroidal degenerations that begin centrally. Here family studies may be essential. These affections still require differentiation.

Retrobulbar neuritis and central choroiditis need to be considered in central lesions without clear genetic background.

IV. TUMOURS

Retinoblastoma

Towards the end of the last century familial occurrence of retinoblastoma began to be reported with increasing frequency, and de Gouvea (1896) recorded the occurrence of the affection in both eyes in three out of seven children born to a man who had lost an eye in infancy from retinoblastoma. A substantial number of pedigrees, mostly showing affected sibships, are now available. From the accumulated literature it appears that there is no high rate of parental consanguinity in affected sibships, that some of the affected sibs are now known to have themselves transmitted the disease, and that there are now many pedigrees with transmission over two or three generations. The available material gives little support for recessive inheritance and suggests dominance with incomplete expressivity and penetrance (Chart 16).

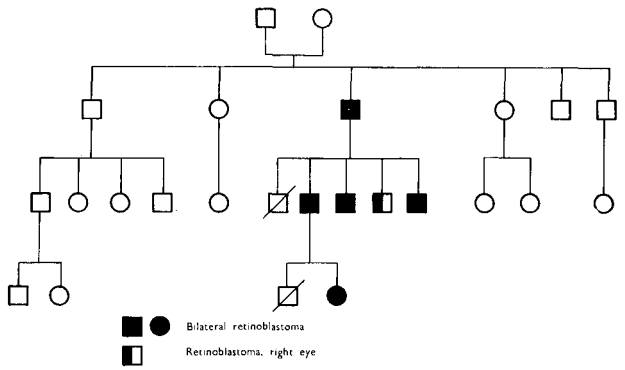

Chart 16. Retinoblastoma. Pedigree showing dominant inheritance (After A. D. Griffith and A. Sorsby, 1944. Brit. J. Ophthal. 28, 279)

Whilst the occurrence of both unilateral and bilateral cases and the occasional occurrence of spontaneous cure add to the difficulties of analysis, it is, however, clear that frankly hereditary cases are exceptional, the sporadic case being the rule.

The highly lethal character of untreated retinoblastoma, and the high mortality of treated cases, raised the possibility that every fresh case of this infantile disease

represented a germinal mutation, and on this assumption Philip and Sorsby (1944) computed the mutation rate at 1.4 X 10^{-5} and Falls and Neel (1951) at 2.3 X 10^{-5}. Vogel (1954, 1957) has questioned the validity of this assumption and holds that germinal mutations account for only a minority of the cases of retinoblastoma, most cases being genuinely sporadic.

Heredity. Most cases of retinoblastoma are unilateral and it is likely that these cases are determined genetically only exceptionally. It is assumed that they represent a somatic mutation. This view is based on the fact that a high proportion of family groups with retinoblastoma show the disease in the bilateral form, whilst the starting point of new lines of retinoblastoma have almost invariably been in survivors who have

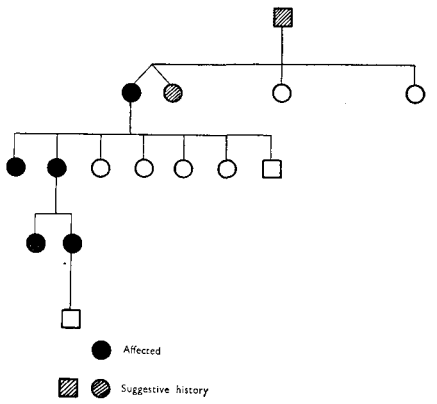

Chart 17. 'Sarcoma' of the choroid. Pedigree showing dominant inheritance (After R. C. Davenport, 1927.Brit. J. Ophthal. 11, 443)

lost both eyes from the affection. It has been computed that the risk of transmission with an apparently sporadic case of unilateral retinoblastoma is of the order of 4 per cent; the risk of transmission is considerably higher in apparently sporadic cases with both eyes affected. The risk of transmission by a member of a known retinoblastoma family, whether affected in one eye or both, is the 50 per cent characteristic of dominance.

'Sarcoma' of the choroid

This has been observed once in two brothers, once over two generations, and twice over three generations. Chart 17 gives the most fully worked out pedigree.

V. OTHER AFFECTIONS

Retinal detachment

No systematic studies are available. There are a number of records of detachment, especially in myopes, over two and three generations. Detachment has also been observed in both members of a pair of uniovular twins who were highly myopic and developed their complication at the age of 40.

Dominant, recessive and sex-linked inheritance have all been recorded. Irregular dominance has also been observed.

The congenital sex-linked form of retinal detachment has been discussed on p. 34.

Uveal reactions

A possible genetic factor in such inflammatory disorders as heterochromic cyclitis, Harada's disease, and the Vogt-Koyanagi syndrome has been suggested on the strength of affected sibships.

SUMMARY

1. Histological studies on the developing retina in mice, rats and Irish setters affected with a hereditary retinal degeneration of the retinitis pigmentosa type do not lend any support to the view that the retina is fully developed before degenerative changes set in — as postulated by the conception of abiotrophy. In fact, the retina in these animals, though reaching functional maturity, lacks the final histological differentiation that leads to fully developed rods: the rods are present, but they are rudimentary and do not survive for the normal span of life. These studies suggest that the abiotrophies (or heredo-degenerative diseases as they are sometimes called) are in fact the mildest of congenital defects and do not therefore stand in sharp contrast to congenital abnormalities.

2. Clinical studies on the hereditary affections of the retina show that the distinction between congenital non-progressive disorders and abiotrophic progressive disorders is not valid. Most congenital abnormalities of the retina such as macular cyst, retinal aplasia, asymptomatic macular defect and congenital sex-linked detachment, show a considerable post-natal course. In fact it is difficult to find a clear example of a congenital non-progressive retinal anomaly. In the choroid, the one substantial congenital defect — macular coloboma — is non-progressive.

3. By definition all abiotrophic defects have a progressive course. This, however, varies considerably in the different affections. In the retina, retinitis pigmentosa represents not one disease but a whole series of affections. This is seen from such well differentiated types as the recessive, dominant, recessive sex-linked and intermediate

sex-linked varieties. Furthermore, in different families there are different associated anomalies, such as glaucoma, cataract, ophthalmoplegia or macular dystrophy. Unilateral retinitis pigmentosa appears to be a somatic mutation. The macular dystrophies are likewise a group rather than one disease, as shown by the different genetic behaviour and the different clinical features of the recessive, dominant and sex-linked varieties of macular dystrophy. Furthermore the ophthalmoscopic reaction ranges in different families from fine granular changes to fairly heavy pigmentary changes, or whitish lesions of the exudative type. In the choroid, choroideremia and choroidal sclerosis — with its generalized, central and peripapillary types — are the two outstanding abiotrophic affections, with markedly dissimilar clinical behaviour.

4. An important abiotrophic affection coming on in middle age is dominant generalized fundus dystrophy with its stormy onset, oedematous and exudative reactions at the macula, and ultimately extensive atrophy throughout the fundus. This has to be distinguished from another dominant affection with a much milder course — Doyne's choroiditis. The choroidal nature of these two affections is not definitely established. They may possibly both be disorders of the membrane of Bruch.

5. Retinoblastoma appears to occur in both a genetic and non-genetic variety. It is likely that the bilateral case represents a germinal mutation and that the unilateral case is generally a somatic mutation; only the germinal mutation is, of course, transmitted.

6. A number of other affections may have a genetic background as yet ill-established.

RIASSUNTO

1. Gli studi istologici sulla retina in fase di sviluppo in topi, ratti e setters irlandesi affetti da degenerazione ereditaria della retina del tipo della retinite pigmentosa non confermano in alcun modo l'opinione che la retina sia completamente sviluppata prima che vi abbiano luogo cambiamenti degenerativi — come viene sostenuto nella concezione dell'abiotrofia. Infatti in questi animali la retina, pur raggiungendo la maturità funzionale, manca della differenziazione istologica finale che conduce ai bastoncelli completamente sviluppati: tali bastoncelli sono presenti, ma sono rudimentali e non sopravvivono per la normale durata di vita. Tali studi suggeriscono che le abiotrofie (o malattie eredodegenerative, come vengono talvolta chiamate) costituiscono in pratica la forma più lieve di difetti congeniti e non sono quindi in contrasto con le anormalità congenite.

2. Gli studi clinici sulle affezioni ereditarie della retina dimostrano che la distinzione fra i disturbi abiotrofici progressivi non è valida. La maggior parte delle anomalie congenite della retina, quali cisti maculare, aplasia della retina, difetto asintomatico maculare, distacco congenito legato al sesso presentano un notevole decorso post-natale. È infatti difficile trovare un chiaro esempio di anomalia congenita non-progressiva della retina. Nella coroide il solo difetto congenito sostanziale — il coloboma maculare — non è progressivo.

3. Tutti i difetti abiotrofici hanno, per definizione, un decorso progressivo. Tuttavia esso varia notevolmente a seconda delle diverse affezioni.

Nella retina, la retinite pigmentosa rappresenta non una malattia ma tutta una serie di affezioni. Lo si vede da tipi così ben differenziati quali il recessivo, dominante, recessivo legato al sesso e intermedio legato al sesso. Inoltre, in diverse famiglie si associano anomalie differenti, quali glaucoma, cataratta, oftalmoplegia e distrofia maculare. La retinite pigmentosa unilaterale appare essere una mutazione somatica. Le distrofie maculari sono piuttosto un gruppo di malattie che non una sola malattia, come è dimostrato dal diverso comportamento genetico e dalle diverse caratteristiche cliniche delle varietà recessiva, dominante e legata al sesso della distrofia maculare. Inoltre la reazione oftalmoscopica varia, nelle diverse famiglie, da leggeri cambiamenti granulari a notevoli cambiamenti del pigmento, o lesioni bianche di tipo essudativo. Nella coroide, la coroideremia e la sclerosi coroideale — con i suoi tipi peripapillari centrali generalizzati — sono le due principali affezioni abiotrofiche con comportamento clinico notevolmente dissimile.

4. Una grave affezione abiotrofica che sopravviene verso la mezza età è la distrofia dominante generalizzata del fundus con attacco violento e reazioni edematose ed essudative alla macula e vasta atrofia finale del fundus. La si deve distinguere da un'altra affezione dominante con decorso più lieve, la coroidite di Doyne. La natura coroidale di queste due affezioni non è definitivamente stabilita. Potrebbero essere ambedue dei disturbi della membrana di Bruch.

5. Il retinoblastoma può essere d'origine sia genetica che non genetica. È probabile che il caso bilaterale rappresenti una mutazione germinale e che il caso unilaterale sia generalmente una mutazione somatica; naturalmente è soltanto la mutazione germinale che viene trasmessa.

6. Alcune altre affezioni possono avere una origine genetica, la quale, tuttavia, non è ancora sufficientemente provata.

RÉSUMÉ

1. Les études histologiques sur la rétine en phase de développement chez des souris, rats et setters irlandais atteints de dégénération héréditaire de la rétine, du genre de la rétinite pigmenteuse, ne soutiennent aucunement l'opinion que la rétine soit complètement développée avant qu'il y aient lieu des changements dégénératifs — comme d'après la conception de l'abiotrophie. En effet, chez ces animaux, la rétine, tout en atteignant la maturité fonctionnelle, manque de la différentiation histologique finale qui amène aux bâtonnets complètement développés: les bâtonnets sont présent mais à l'état rudimentaire et ne survivent pas pour la durée normale de la vie. Ces études suggèrent que les abiotrophies (ou maladies hérédo-dégénératives, comme on les appelle parfois) constituent pratiquement la forme la plus légère de défaut congénital et ne sont donc pas en contraste avec les abnormalités congénitales.

2. Les études cliniques sur les affections héréditaires de la rétine démontrent que la distinction entre troubles congénitaux non-progressifs et troubles abiotrophiques progressifs n'est pas valide. La plupart des abnormalités congénitales de la rétine, telles que le kyste maculaire, l'aplasie de la rétine, le défaut asymptomatique maculaire, le détachement congénital sexe-linké de la rétine démonstrent un considérable décours post-natal. Il est en effet malaisé de trouver un exemple clair d'anomalie congénitale non-progressive de la rétine. Dans la choroïde le seul défaut congénital important — le colobome maculaire — est non-progressif.

3. Par définition, tous les défauts abiotrophiques ont un décours progressif. Cependant ceci peut varier selon les diverses affections. Dans la rétine, la rétinite pigmenteuse représente non pas une maladie mais plutôt une série d'affections. On peut s'en apercevoir par des types si bien différenciés tels que le récessif, le dominant, récessif sexe-linké et l'inter-moyen sexe-

linké. En plus, chez plusieurs familles l'on trouve de différentes anomalies associées, telles que glaucome, cataracte, ophtalmoplégie ou dystrophie maculaire. La rétinite pigmenteuse unilatérale semble être une mutation somatique. Les dystrophies maculaires sont un groupe de maladies plutôt qu'une seule maladie, comme il est démontré par le comportement génétique divers et par les diverses caractéristiques cliniques des variétés récessive, dominante et sexe-linkée de la dystrophie maculaire. En plus, la réaction ophtalmologique varie, chez les diverses familles, de légers changements granulaires à remarquables changements du pigment, ou lésions blanches de type exudatif. Dans la choroïdienne — avec ses types péripapillaires centrales généralisés — sont les deux affections abiotrophiques principales avec un comportement clinique remarquablement différent.

4. La dystrophie dominante généralisée du fond de l'œil est une importante affection abiotrophique survenant vers l'âge moyen, avec début violent et réactions édémateuses et exudatives de la macule et vaste atrophie finale du fond. Il faut la distinguer d'une autre affection dominante avec décours plus léger, la choroïdite de Doyne. La nature choroïdienne de ces deux affections n'a pas encore été définitivement établie. Dans les deux cas il pourrait s'agir de troubles de la membrane de Bruch.

5. Le rétinoblastome peut avoir une origine soit génétique que non-génétique. Il est probable que le cas bilatéral représente une mutation germinale et que le cas unilatéral représente, en général, una mutation somatique. Naturellement, ce n'est que la mutation germinale qui est transmise.

6. Quelques autres affections peuvent avoir une orgine génétique qui n'est, toutefois, pas encore tout-à-fait démontrée.

ZUSAMMENFASSUNG

1. Histologische Studien über die Retinaentwicklung an Mäusen, Ratten und irischen Setters, die an einer erblichen Netzhautdegeneration des Types der Retinitis pigmentosa litten, unterstützten die Ansicht, dass die Netzhaut bevor die degenerativen Veränderungen einsetzen — wie das Konzept der Abiotrophie es fordert — völlig entwickelt ist, nicht. Denn obwohl die Netzhaut bei diesen Tieren die Funktionsreife erreicht, so fehlt ihr doch die endgültige histologische Differentiation, die völlig entwickelte Netzhautstäbchen mit sich bringt: diese sind zwar vorhanden, aber sie sind rudimentär und überleben nicht die normale Lebensdauer. Diese Studien zeigen, dass die Abiotrophien (oder degenerativen Erbkrankheiten, wie man sie manchmal nennt) in der Tat die leichtesten angeborenen Fehler sind und somit zu den angeborenen Abnormalitäten in keinem scharfen Gegensatz stehen.

2. Klinische Untersuchungen über die erblichen Netzhautaffektionen zeigen, dass die Einteilung in angeborene, nicht-progressive Störungen and abiotrophische progressive Störungen nicht gültig ist. Die meisten angeborenen Netzhautabnormalitäten, wie die Macularcyste, die Netzhautaplasie, der asymptomatische Macularfehler und die angeborene geschlechtsgebundene Netzhautablösung, weisen einen bemerkenswerten post-natalen Verlauf auf. Es ist in der Tat schwer, ein deutliches Beispiel von angeborener, nichtprogressiver Netzhautanomalie zu finden. Das Coloboma macular — der einzige wesentliche angeborene Fehler der Aderhaut — ist nichtprogressiv.

3. Alle abiotrophischen Fehler haben, wie das Wort es besagt, einen progressiven Verlauf. Dieser ist jedoch bei den einzelnen Affektionen sehr verschieden. In der Netzhaut stellt die Retinitis pigmentosa nicht eine einzelne Krankheit sondern eine ganze Reihe Affektionen dar. Das zeigt sich aus der klaren Differentiation der verschiedenen Typen: rezessiv, dominant, rezessiv geschlechtsgebunden und intermediär geschlechtsgebunden. Je nach der Sippe gesellen sich ausserdem verschiedene Anomalien dazu,

wie Glaukome, Star, Ophthalmoplegie oder Dystrophia macular. Die einseitige Retinitis pigmentosa scheint eine somatische Mutation darzustellen. Die Dystrophiae macular, sind ebenfalls eher eine Gruppe als eine einzige Krankheit, wie aus dem unterschiedlichen Erbverhalten und den verschiedenen klinischen Anzeichen der rezessiven, dominanten und geschlechtsgebundenen Abarten derselben hervorgeht. Die opthalmoskopische Wirkung erstreckt sich ausserdem in den verschiedenen Familien von feinen granulären bis zu ziemlich schweren Pigmentveränderungen oder gar weisslichen Läsionen exsudativer Art. In der Aderhaut sind die Choroideremie und die Choroidalsklerose — mit ihren generalisierten, zentral peripapillaren Typen — die beiden wichtigsten abiotrophischen Affektionen mit wesentlichen Unterschieden im klinischen Verhalten.

4. Eine wichtige abiotrophische Krankheit, die in mittlerem Alter auftritt, ist die dominante generalisierte Fundusdystrophie, die sich durch ihren stürmischen Beginn, die ödematösen und exsudativen Reaktionen an der Macula und schliesslich extensiven, über den ganzen Fundus gehenden Atrophie auszeichnet. Diese ist nicht mit einer anderen dominanten Krankheit mit leichterem Verlauf — der Choroiditis nach Doyne — zu verwechseln. Die choroidale Natur dieser beiden Affektionen ist noch nicht definitiv festgestellt. Vielleicht sind beide Störungen der Bruchschen-Membran.

5. Das Netzhautblastom scheint sowohl als erbliche wie auch als nicht erbliche Form aufzutreten. Es ist möglich, dass der bilaterale Fall eine Germinalmutation und der einseitige Fall gewöhnlich eine somatische Mutation ist; natürlich wird nur erstere vererbt.

6. Mehrere andere Krankheiten haben möglicherweise einen erblichen, bis jetzt noch nicht genau festgestellten Hintergrund.

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