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COMMUNICATIONS

CONGENITAL COLOBOMA OF THE MACULA: TOGETHER WITH AN ACCOUNT OF THE FAMILIAL OCCURRENCE OF BILATERAL MACULAR COLOBOMA IN ASSOCIATION WITH APICAL DYSTROPHY OF HANDS AND FEET

BY

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IN 1852 von Ammon described the pathological appearances of an eye with coloboma of the iris and other changes suggestive of what now would be called coloboma of the macula. Though the fovea was present, the macular area had a defect in the choroid, 1 inch by 0·5 inch, partially closed by a tissue poorly supplied with vessels. Ophthalmoscopically the first record comes from Streatfeild in 1866, who reported a typical case of unilateral macular coloboma as an unusual variation of posterior staphyloma seen in myopia. The recognition that the defect is of congenital origin and not the result of myopia came independently from Reich and de Wecker in 1870—not without a controversy in 1872 as to priority. The term *coloboma* as applied to this lesion was intoduced by Reich; Hirschberg in 1875 used the name of *Dictyoschisma centralis*, whilst Wiethe in 1885 employed the term *Staphyloma of the sclerotic in the macular area*. The first bilateral

case to be reported was by Schmidt-Rimpler in 1880; more convincing cases came in 1898 from Kastalsky and from Kimpel. The familial incidence of the affection was first noted independently by Schott and by Clausen in 1921, whilst in the present paper, a familial skeletal defect is reported in association with the familial occurrence of macular coloboma.

I.—Review of Literature

An analysis of the literature on coloboma of the macula is not facilitated by the rather loose way in which the term, itself unsatisfactory, is used. Many cases are clearly not congenital defects or not central in position; others are equally clearly cases of a different entity—traumatic macular holes, nondescript lesions of indefinite origin and even central choroiditis with heaped up exudate. A further number of cases had to be omitted from consideration as they are incompletely described (being generally mentioned in transactions of societies); whilst a few had to be discarded for technical reasons, the original reports not being available. Reference to these discarded cases is made under a separate heading in the bibliography.

The sifted material left 21 cases of bilateral macular coloboma, 36 unilateral, 3 (and possibly 5) familial groups, and 16 cases having some bearing on the condition.

1. *Bilateral coloboma.*—Excluding the familial groups, which will be considered separately, 21 cases—11 male and 10 female—are available. Low errors of refraction or emmetropia is recorded in many cases; high hypermetropia (right eye 12D., left eye 11D.) was present in the case of Schmidt-Rimpler, high astigmatism (6·0D.) in one case (Feilchenfeld) and high myopia in the cases of Kimpel, Car and of Clarke. Vision in the neighbourhood of 6/60 is the most frequent, but 6/24 and even 3/4 (Feilchenfeld) and 5/6 (Schmidt-Rimpler) are recorded. The presence of central scotoma is noted by Kastalsky, Agaston and Shoji; that no central scotoma was present is reported by Schmidt-Rimpler, Kimpel, Van der Hoeve, and Oeller. The size of the macular coloboma was generally about 3D.D. by 3D.D. (disc diameters) or rather less, and excavation about 3D. A coloboma 9 by 10D.D. is recorded by Kimpel; absence of excavation is noted by Schmidt-Rimpler and Hoeg, whilst excavation of 7D. is reported by Shoji; excavation of 10D. in some parts of the coloboma is noted by Oeller. Eleven of the 21 cases had non-pigmented colobomata; the complete absence of pigment was, however, exceptional, as scattered fine pigment or streaks of pigment extending from the margin were generally present. A varying degree of marked pigmentation was present

in the remaining 10 cases. In most cases the margin was sharp and highly pigmented. The presence of varying amounts of choroidal vascularization is noted by practically all observers, short posterior ciliary vessels being noted by Kimpel, ? scleral vessels by Kastalsky, intact large choroidal vessels by Weeks. Only three observers note the complete absence of vessels (Schmidt-Rimpler, Oeller and Lemke). Practically all observers note the passing of retinal vessels over the coloboma; negative findings on this head are reported by Przybylska and by Dollfus. Outlying small colobomatous areas were observed by Lemke, and larger ones by Lindsay Johnson; an outlying patch of atrophy is noted by Oeller.

That there was no consanguinity is noted by Car and by Dollfus; a large head is noted by Hansell, microcephaly by Car, bad development of face by Clarke; mental deficiency was observed by Pierce; horizontal nystagmus under voluntary control by Shoji; pale discs by Hansell, Lemke and by Appleman; coloboma of the disc and atypical pupillary membrane by Oeller. Three further congenital defects were noted—a little finger shorter than normal was present in Car's case, undescended testes in Clarke's and "other congenital defects, including ears standing out" by Feilchenfeld.

(Schmidt-Rimpler's case is included in this series rather as an act of piety towards the first case of bilateral coloboma described. It is doubtful whether a lesion without excavation can be regarded as coloboma; even if so regarded, the paramacular situation of the lesions, allowing for 5/6 vision in an affected eye, should really place this case amongst the group of unilateral coloboma with associated paramacular coloboma.)

2. *Unilateral cases.*—Of the 36 cases of this type, with the incomplete data on some of them, the following analysis is possible:—

Sex.—Males, 19; females, 13.

Eye affected.—Right, 17; left, 13.

Type.—Pigmented, 9 (Schnabel, von Hippel, Oeller, Lewis, Krawtschenko, Dutoit, Lister, Lederkarl cases 2 and 4); non-pigmented, 23 (including 12 in which fine scattered pigment was present). The margin would appear to have been deeply pigmented in practically all cases.

Scotoma.—The presence of a scotoma is noted in eight cases; that a scotoma was not present is noted in one (Meyer, 1885).

Vessels.—(*a*) *Choroidal.*—Complete absence of choroidal vessels is noted three times (de Wecker, Meyer and Horton); the presence of choroidal vessels is noted 13 times. Streatfeild speaks of short posterior ciliary vessels breaking up in the coloboma.

(*b*) *Retinal.*—In most cases the retinal vessels do not pass over

the coloboma. That the retinal vessels dip into the coloboma is noted four times (Remak, Debierre, Van Duyse, Poljak).

Extent.—All but one were irregularly circular areas, ranging from about 2 to 4 D.D. in size. In Horton's case it was only 0·5 D.D. large.

Excavation.—5 D. is reported by Debierre, 6·0 D. by Hunneman, and 13D. by Preobraschensky. Slight excavation is reported in most of the pigmented colobomata.

Refraction.—Myopia is noted 9 times, including the cases of Schnabel (-1·0 D.), Meyer (-3·0 D.), Rumzewicz and of Oeller (-5·0 D.). Hypermetropia is noted seven times, including the case of Goulden with 9·0 D. (in a microphthalmic organ).

Visual acuity.—Most reports give a high degree of visual defect for the affected eye. However, vision of 1/5 given by de Wecker and 20/100 by Lewis; 6/36 is given twice (Lindsay Johnson, Silcock).

Unilateral colobomata associated with other defects.—Fourteen of the 36 cases of unilateral macular coloboma presented points of special interest.

(*a*) *Associated para-macular coloboma.*—The simplest variety of associated defect is another coloboma similar in all respects except for its position. Meyer (1884) records a macular coloboma in the right eye with vision reduced to finger counting at 0·5 metre; in the left eye a very similar lesion was situated just external to the macula; with correction vision was 6/6. Lindsay Johnson (cases 1 and 2) reports a similar case except that the paramacular lesion was situated further out.

(*b*) *Associated with typical choroidal coloboma.*—Typical choroidal coloboma in both eyes with macular coloboma in the right is reported by Horton. Unilateral coloboma of choroid and optic nerve with macular coloboma is noted by Wood in a microphthalmic eye. Reiss reports choroidal coloboma in the left eye—which was also the seat of dense fibrous tissue in the vitreous—whilst the right showed macular coloboma, together with two other circumscribed areas, and absence of inferior nasal artery and vein. The presence of macular coloboma in one eye and choroidal coloboma in the other is also reported by Menacho.

(A parallel case for coloboma of the iris, one eye showing a typical iris coloboma and the other an atypical one, is reported by Rössler.)

(*c*) *Associated with colobomatous defects.*—In Lister's case, a typical macular coloboma was present in the left eye; in the right eye there was a sharply circumscribed circular defect downwards. Macular coloboma in one eye and coloboma of the optic disc in the other is noted by de Wecker (1876), whilst the association of the two in the same eye is observed by Goulden,

whose case also showed microphthalmos and persistent pupillary membrane. Tarnowski's case showed a reniform optic disc with the defect directed towards the macular coloboma. As already noted under (*b*), multiple colobomatous defects were present in Reiss' case. Multiple lesions were also present in Lederkarl's case.

(Socolova reports multiple colobomatous defects in association with typical choroidal coloboma.)

(*d*) *Associated with vascular abnormality.*—In Silcock's case a connective tissue strand extended forward from the centre of a non-pigmented macular coloboma towards the lens capsule. A case in which two vessels, believed to belong to the ciliary group, and springing from the centre of a macular coloboma is reported by Genet.

(Vessels in connection with non-macular coloboma have been reported by Beaumont, by Mann and Ross and by Lederkarl, [case 2.])

(*e*) *Microphthalmos.*—As already noted this was present in the cases of Wood and of Goulden.

(Damos, read in abstract, also reports this association.)

(*f*) *Mental deficiency.*—This was observed in the case of de Wecker (1876). (In a case of bilateral macular coloboma this was observed by Pierce.)

(*g*) *Other defects.*—Sokolow, as reported in abstract, saw the following combination:—(1) Conjunctival dermoid; (2) coloboma of the macula, and (3) large tumour of the forehead and cheek—all on the same side.

3. *Familial cases.*—Since the first reports on familial cases by Schott and by Clausen in 1921, other familial groups have been reported.

Schott's patients are two sisters, aged 7 and 8 years respectively, showing bilateral pigmented macular coloboma, or more strictly paramacular coloboma. The younger child was hypermetropic (1·5 D.e.e.), and vision was, right eye, 5/36; left eye, 5/18. The older sister had almost identical lesion; she had astigmatism 5·0 D. in the right eye and 3·0 D. in the left. There was no central scotoma. Choroidal vessels could be seen amidst the pigment in the coloboma.

Clausen's family group consist of a man and his two sons affected with bilateral macular coloboma. The father's sister has "typical macular coloboma" and two of her daughters are likewise affected.

Davenport's group consists of mother and son showing bilateral symmetrical macular coloboma allowing 6/24 vision. The mother's colobomata are flat and pigmented, the son's colobomata are less pigmented and more excavated.

Less convincing is the group reported by Leonardi. Macular

colobomata were present in four brothers, out of a sibship of 9. The parents are healthy and normal, not consanguineous, but the mother's Wassermann reaction is positive. In the affected children a coloboma is present in highly myopic eyes (12 D. to 16 D.), and the following associations are also present:—

In all the four. Choroidal lesions and nystagmus.

In three. Ectopia of the pupil.

In two. Microphthalmia and atrophy of the iris.

In one. Tremulous iris.

The significance of this last group, as also the group of three sisters with macular lesions reported by Blank, is not clear; both these groups are reported in abstract.

4. *Paramacular coloboma.*—A number of macular colobomata reported as such belong to this group. The cases of Beaumont and of Schmidt-Rimpler (1899) are illustrations of a unilateral lesion of this type, both with poor vision. Bilateral paramacular colobomata with full vision in each eye are reported by Lindsay Johnson (case 6) and by Sorsby, whose case showed latent nystagmus. In contrast to these cases in which the paramacular defect was situated temporally, there are the cases of Michaelson and Van Lint, in which a defect in the central area involved the optic nerve; these cases are only doubtfully cases of macular coloboma. A paramacular coloboma in one eye, and in the other eye two colobomata reminiscent of choroidal coloboma and situated above and below the disc respectively, is reported by Forsmark.

5. *Wheel-figure type of macular coloboma.*—The macular coloboma present in his case is thus described by Lister:—

"At the macular region there is a large, sharply-defined, oval area, dark in the centre and white at the periphery. The latter is divided by pigmented bands, which pass from the centre to the margin. The centre . . . and the pigmented bands are on the same level as the surrounding retina, whereas the peripheral white areas are deeply depressed."

Ten years earlier Lindsay Johnson had described and illustrated similar appearances in two cases (Nos. 2 and 11 of his series), whilst Clarke's case of bilateral coloboma is in many respects very similar. Seefelder's bilateral case, reported briefly, would appear to be of the same type: a central disciform area, white and excavated is surrounded by a brown margin, from which pigment striae spread out like the spokes of a wheel, and go towards a rim of pigment, itself the final margin of the coloboma.

These cases are of interest for comparison with the four cases reported by Deutschmann in 1920. Under the title "A peculiar, probably congenital lesion at the macula," he reports the presence of a wheel-figure, occurring once bilaterally and three times unilaterally. In the first case the Wassermann reaction was positive,

in the second there was suspicion of a tuberculous constitution; in the remaining two, no evidence of systemic disease. In all the four maldevelopmental lesions were present. Some excavation of the wheel-figure area was present in all the four cases, but Deutschmann says that the macular appearance "has nothing in common with the well-known picture of macular coloboma," and that the appearances seen are new to him. (He must have overlooked Lindsay Johnson's cases reported in 1890 and Lister's case in 1900.) Deutschmann argues that the lesion is caused by intra-uterine inflammation.

Whether these cases constitute a special type of macular coloboma cannot be said on the present evidence. At any rate, they constitute an interesting and easily recognized variety of pigmented coloboma, and Deutschmann's term of wheel-figure is not inapt. One such lesion is figured, but not described, by Hoeg (case 3). A wheel-figure also appears to have been present in one of Lederkarl's cases (No. 2).

Comment on the clinical appearances of macular coloboma.—A perusal of the literature gives one little guidance by which an excavated lesion at the macula can be definitely diagnosed as a macular coloboma of congenital origin. The presence of pigment cannot be regarded as evidence of inflammation, as the familial cases show, and as is also borne out by the graduation between complete lack of pigment and massive proliferation. The presence of outlying white or pigmented areas is not conclusive proof of an inflammatory reaction, whilst excavation is not an absolute factor in favour of the congenital origin of the lesion, for excavation may be quite mild in congenital cases and marked excavation may be present in areas atrophic from old inflammation. A rolled, sharp margin is, perhaps, the least unreliable of all signs. Whilst the earlier literature contains, in addition to reports on non-pigmented deeply excavated colobomata, many cases of excavated lesions that would now be regarded as frankly inflammatory, recent literature contains reports of pigmented colobomata in which excavation appears to have been a subsidiary feature. Davenport's familial group, the mother's colobomata being flat and pigmented, and the son's less pigmented and more excavated, probably illustrates a genuine characteristic. The decision as to whether a given lesion is a congenital macular coloboma represents not a statement of fact, but a judgment on summed-up evidence.

6. *Pathological Anatomy.*—The literature contains seven histological reports, none of them free from objection, and none, barring the doubtful exception of Deyl's case (and ? Janku's case), referring to a case observed clinically.

(1) Bock (1885). This report concerns the accidental discovery of ectasia at the posterior pole of the two eyes in a man who

died, aged 32 years, from pneumonia. No clinical details were available.

(2) Deyl (1898). In a boy who died, aged 5 years, there was hydrocephalus and cleft palate. Clinically there had been observed pale discs in both eyes and a central non-excavated lesion 5 D.D. wide in the left eye; in between this lesion and the disc there was a pale red area with greyish lesions containing vessels.

(3) Van Duyse (1898). In this case a cyclopean eye with two lateral (macular) colobomata forms the basis of the report.

(4) Parsons and Coats (1906). In a female child there was observed at birth an orbital swelling which ultimately led to the death of the child after operation at 9 months. Clinically the right eye was smaller than the left and showed coloboma of the optic nerve, together with other fundus abnormalities "difficult to examine, and the interpretation . . . also difficult." Post-mortem the orbital tumour proved to be an encephalocele, growing from a highly abnormal brain, whilst the eye defects consisted of (1) a cystic bulging on the nasal side of the disc; (2) a large coloboma of the nerve entrance, and (3) "a defect of pigment epithelium in the macular region corresponding with the white patch seen with the ophthalmoscope in this situation;" the fovea itself was intact.

(5) Janku (1923). Only an abstract of this article published in Hungarian was available. In a child, aged 11 months, bilateral coloboma was present, one eye was smaller than normal. It would appear that, histologically, widespread lesions were found. Janku interprets his findings as showing inflammatory reaction, and holds the inflammation to be caused by parasites 20μ to 30μ in size. Seefelder, on whose abstract this paragraph is based, doubts whether the case was one of macular coloboma.

In addition to these reports there are the histological findings reported by Hess for the right eye of a rabbit, and by Zimmermann for the left eye of a dog.

These anatomical studies of doubtful material do not go beyond the finding of absence to varying degrees of the pigment epithelium, choroid and retina, except that in Parsons and Coats' case the defect was confined to the pigment epithelium only. Deyl held that his case supports the view of Lindsay Johnson, that colobomata are caused by choroidal naevi. Reviewing the cases of Bock, Deyl, Hess and Zimmermann, Ida Mann in 1926 concluded that they present evidence in favour of macular coloboma being due to intra-uterine inflammation—a reading that is not warranted either by the validity of the material or the findings reported.

7. *Theoretical considerations.*—The older views on the causation of macular coloboma can be dismissed briefly as they have been dealt with by Parsons in 1906 and by Ida Mann in 1927, whilst the arguments in favour of secondary fissures as the cause of atypical coloboma have been reviewed recently by Rones.

(1) *Developmental failures.*—One view was the attempt to link up macular coloboma with typical choroidal coloboma by assuming that the macula is developed in the choroidal cleft which by rotation comes to lie horizontally. Apart from the fact that embryologists no longer admit this theory of rotation, the existence of both macular coloboma and typical choroidal coloboma in the same eye (cases of Wood and of Horton) invalidates this argument.

Other embryological theories postulate localized failure in the neural ectoderm, or in the pigment layer, as also abnormal development of the mesoderm. Treacher Collins implicated localized absence of posterior ciliary vessels, thus regarding colobomata as localized choroideremia.

(2) *Inflammation.*—That some macular "colobomata" are of post-natal origin cannot be doubted. The tuberculous nature of some of these lesions has been demonstrated by Funccius, by Meisner and by Harrison Butler amongst others. It is argued that intra-uterine inflammation explains the others. Ida Mann holds the pigmented coloboma to represent irritative and the non-pigmented destructive lesions.

(3) *Trauma.*—Trauma is a factor in macular changes that are hardly distinguishable from colobomata. The cases of Lagrange and the illustrations in Würdemann can be instanced. That birth injuries and haemorrhage are the cause was suggested by a number of observers.

(4) *Naevus formation.*—Lindsay Johnson held that atypical colobomata represent choroidal naevi in varying stages of shrinkage. The indented edge and lobulated appearance of some lesions he held to be evidence in support of this view. As already mentioned Deyl held that the histological appearances in his case supported Johnson's theory. More recently this view has been upheld by Hoeg.

None of these theories is free from serious objection, Treacher Collins' view probably being the least unsatisfactory. The hereditary nature of macular coloboma militates against such factors as inflammation and trauma, whilst the failure to explain macular coloboma on a developmental basis raises the question whether it is possible to regard these colobomata as instances of arrested development. In this connection, the evidence of experimental embryology, bringing out the association of ocular and skeletal defect are of the utmost interest and will be considered separately after the report on the cases of familial coloboma with skeletal abnormalities.

II.—Case Reports on the Familial Recurrence of Macular Coloboma with Skeletal Defects of Hands and Feet

1. *Family history.*—The family consists of the parents and seven children. The mother and five of the children are the subjects of this report. The father and the two remaining children are healthy. The parents are not of consanguineous stock; they are English, are both London born and derived from families that have lived in London as far as they can trace them back. There is no history of visual defect, mental trouble or bodily deformity in the antecedents of either of the parents.

The mother's antecedents and personal history.—The father, a bricklayer by occupation, died at 72 years of age; the mother at 68 years of age. There were five brothers and five sisters, all of them, barring the patient, without visual or physical defect. The patient herself had poor sight since childhood, but attended an ordinary Board School and held her own in class. She married at 20 years of age, had eight children and two miscarriages. Apart from frequent headaches, she has always enjoyed good health. The order in the family is as follows:—

1. Elizabeth, aged 38 years. Single.

2. Miscarriage.

3. Henry James, died at 1 year 7 months. He was a very quiet child, with deformed hands and feet, which used to swell up frequently. "The lips were like a bunch of grapes." "One ear became mortified," and the child died of "cancer of the head."

4. Harry, aged 34 years. Normal. Is married and has four children, three boys and one girl; all well.

5. Alfred, aged 29 years. Affected.

6. Edward, aged 25 years. Affected.

7. Charles, aged 22 years. Affected.

8. Florence, aged 20 years. Normal. Is married and has a boy who is normal.

9. Miscarriage.

10. James, aged 16 years. Affected.

2.—*Investigations.*—The mother, Alfred (No. 5 in the list) and James (No. 10) were exhaustively examined as in-patients of the London Jewish Hospital (the patients are not Jews); Edward and

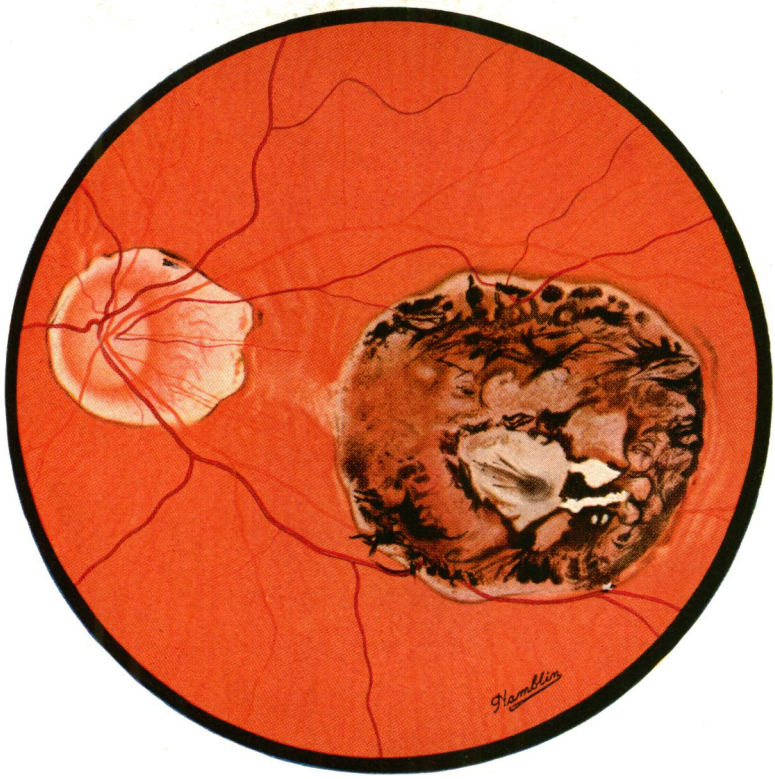


FIG. 2.

Fundus of Mrs. S.

Note.—(1) Circumpapillary myopic atrophy. (2) Extent and sharp delineation of central lesion. (3) The rolled appearance of the edges in part of their course. (4) The passing of retinal vessels over the lesion. (5) The uneven distribution of pigment over the lesion. (6) Depression of the centre, particularly well seen in the left eye.

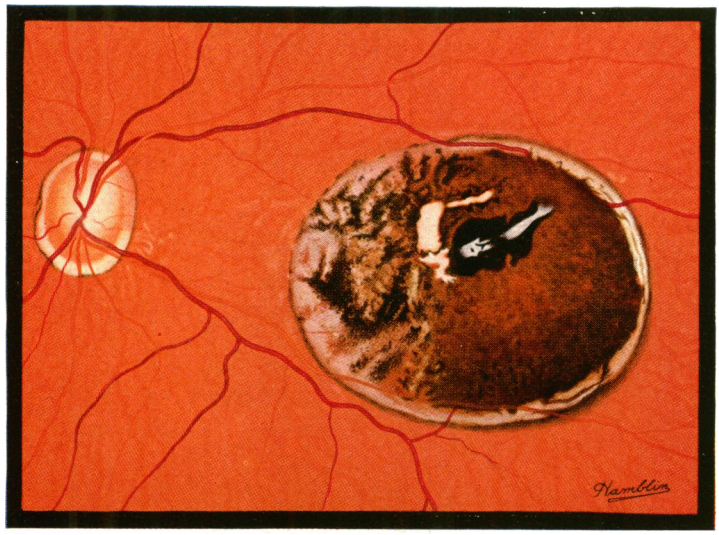
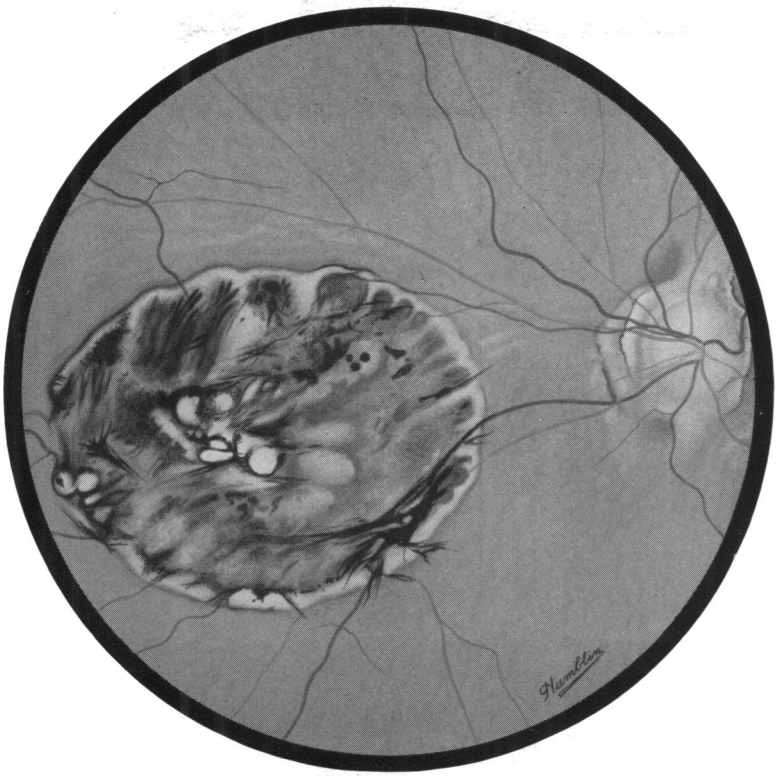


FIG. 10.

Fundus of James

Note.—(1) The deep excavation of these two lesions. (2) The high degree of pigmentation.



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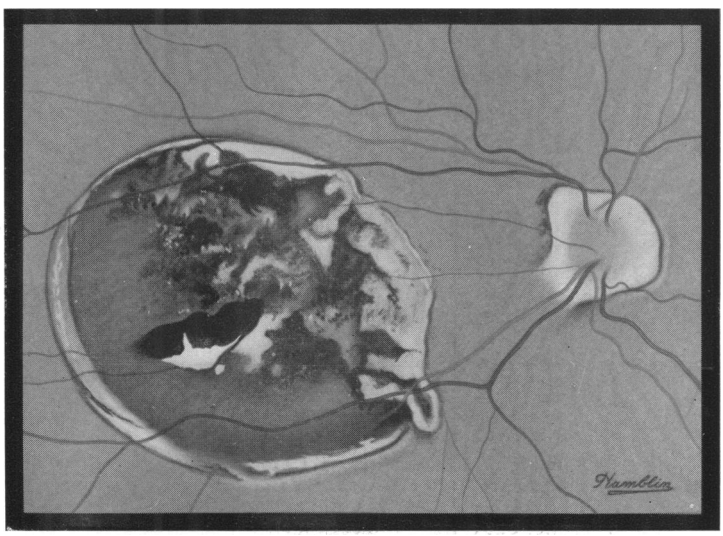

FIG. 9.

Fundus of James

Note.—(1) The deep excavation of these two lesions. (2) The high degree of pigmentation.

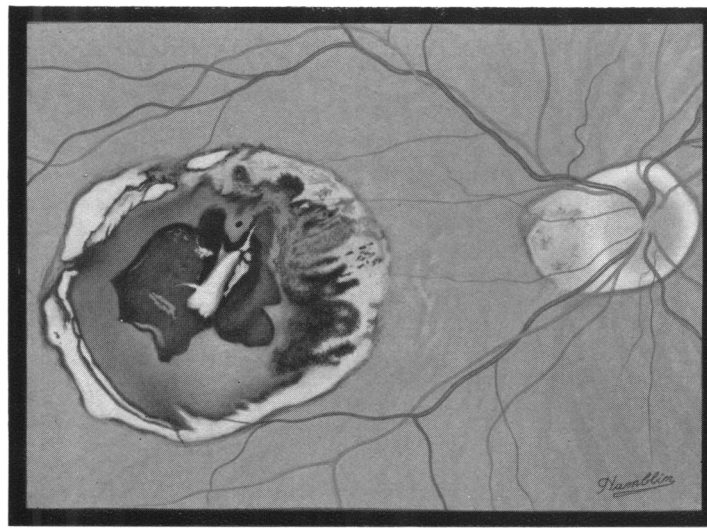

FIG. 3.

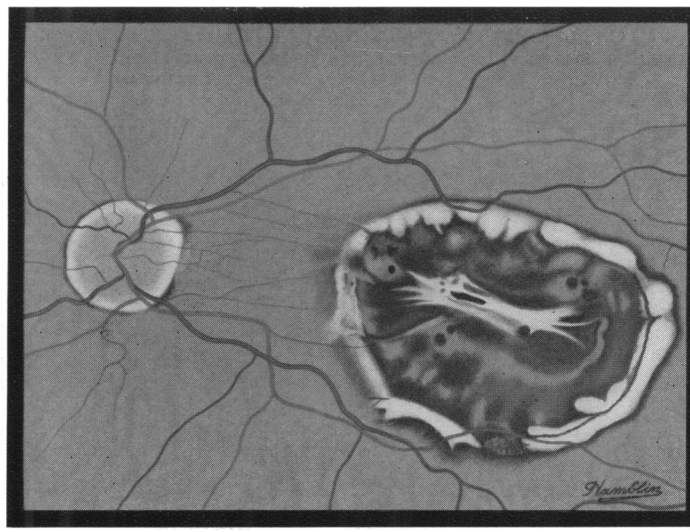

FIG. 4.

Fundi of Alfred

Note.—(1) The highly rolled edges. (2) The marked depression in the centre. (3) The excessive presence of white tissue (which, on the edges, did not appear to be exposed sclerotic, but raised fibrous tissue).

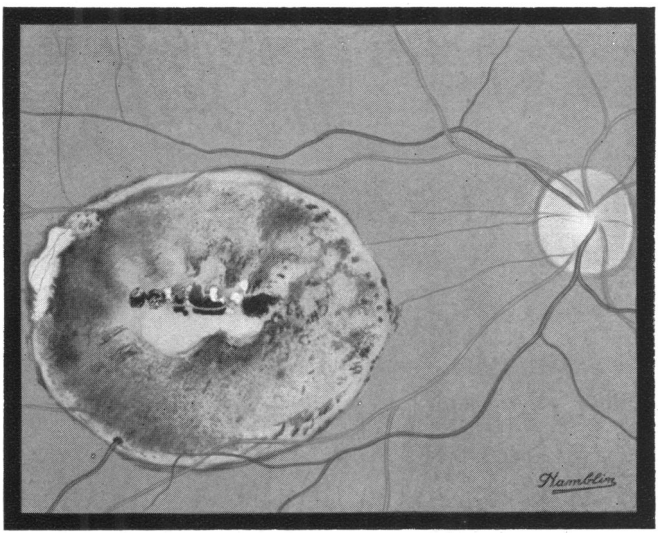

FIG. 5.

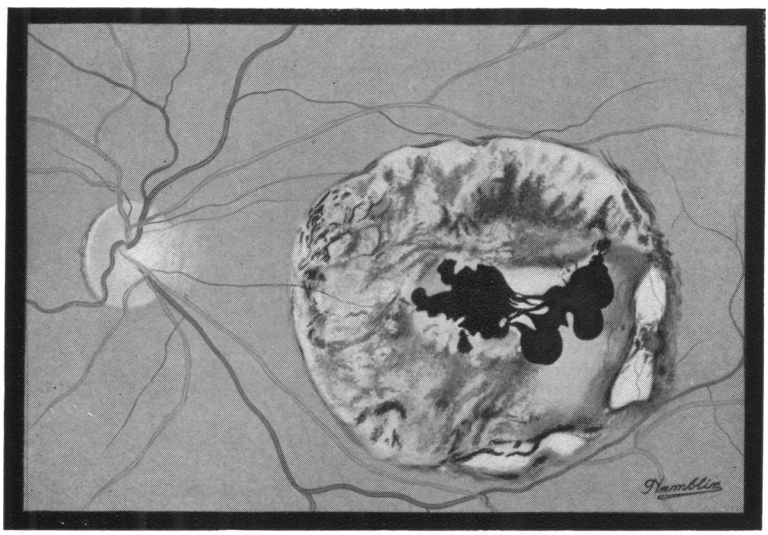

FIG. 6.

Fundi of Edward

Note.—(1) The irregularity of the depression, particularly seen in the right eye at the lower margin. (2) The relative absence of pigment, allowing a few choröidal vessels to be seen.

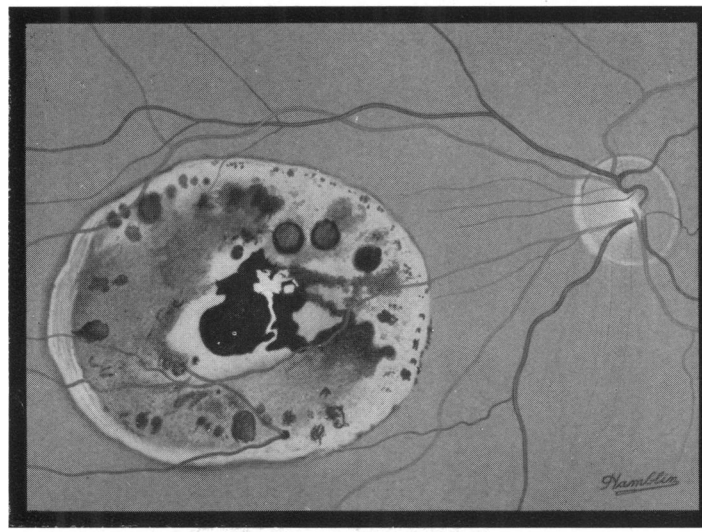

FIG. 7.

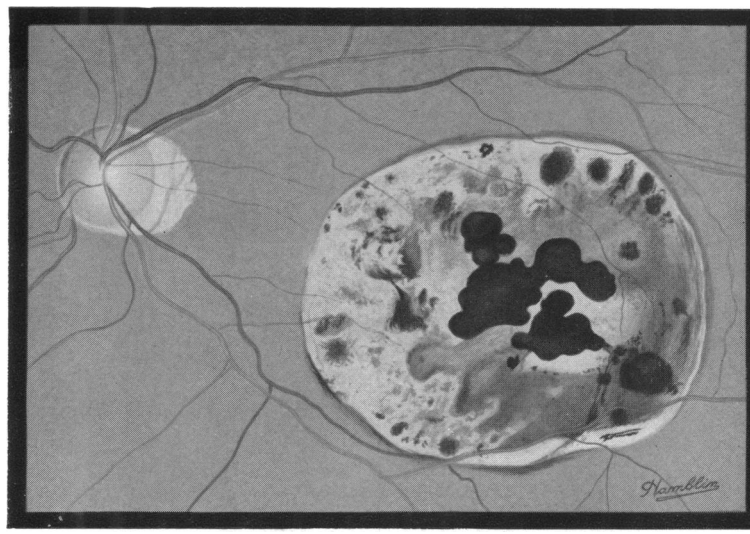

FIG. 8.

Fundi of Charles

Note.—(1) Rolled edges, particularly in the left on the temporal side. (2) The relative paucity of pigment in the periphery of the lesion. (3) The unmasking of choroidal vessels. (4) The springing of what looks like a retinal vessel from a pigmented point at the lower margin of the lesion of the left eye.

Charles were seen on several occasions and Elizabeth twice. The normal members of the family and their normal descendants were also seen. The mother, Elizabeth, Edward, Charles and James were shown at the Ophthalmological Section, Royal Society of Medicine, on January 12, 1934.

3. *Factors in common in the affected members.*—(1) Rudimentary nails on the index finger of each hand and on the big toe of each foot.

The nails are either completely absent or are indicated by two grooves situated on either side of the centre of what is normally the nail bed. This appearance is seen throughout, except that a badly developed nail is present on the index finger of James' right hand.

(2) Abnormal appearance of the terminal part of the thumb and of the big toe. This ranges from a practically normal thumb, in the case of the mother and Elizabeth, to complete bifurcation of the thumb as in the case of Alfred. In all the patients the end of the big toe is wide.

(3) A uniform skeletal defect as revealed by X-ray. Essentially the changes seen on X-ray are (1) tendency to diminution or actual suppression of the second phalanx of the little finger; (2) a tendency to bifurcation of the terminal phalanx of the thumb; (3) bifurcation in all but Alfred of the terminal phalanx of the big toe; (4) a tendency to considerable atrophy of the terminal phalanges of both hands and feet. In addition, Alfred's right foot shows complete suppression of the small toe (see Figs. 11-20).

(4) Bilateral pigmented macular coloboma. In size there is a general resemblance between these various lesions, being approximately 5 to 6 D.D. by 3 to 4 D.D. large, with the larger diameter horizontally placed. The margins of all the lesions are sharp and in contrast to the cases recorded in the literature there is no greater heaping up of pigment at the margin than in the centre. The degree of pigmentation varies considerably, though none of the lesions could be regarded as a non-pigmented coloboma. In the less pigmented lesions choroidal vessels could be seen. Retinal vessels are seen passing over all the colobomata. Excavation is variable from case to case and in the same lesion from place to place, generally being most marked in areas relatively free from pigment. All the colobomata thus show some degree of excavation and none of them an excavation more than two dioptres at any particular point. Whilst there is a strong family likeness throughout, the two colobomata in any given patient have a greater resemblance to each other than to the lesions in the other members of the family (Figs. 1-10).

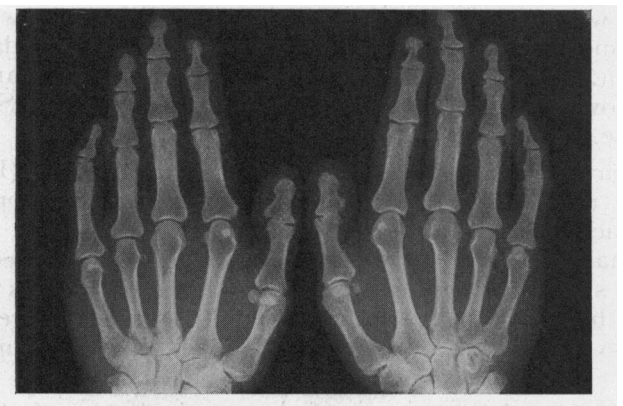

FIG. 11.

Hands of Mrs. S.

Note.—(1) Bulbous extremity of terminal phalanx of thumbs. (2) Deformity of small finger involving stunting of the 2nd phalanx.

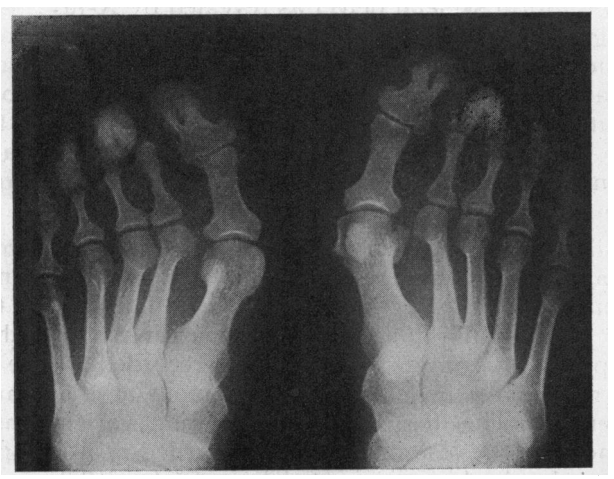

FIG. 12.

Feet of Mrs. S.

Note.—(1) Bifidity of terminal phalanx of big toe. (2) Deformity of 2nd and 3rd phalanges of other toes.

4. *Individual case histories.*

(*a*) *Mrs. Helen S.*, aged 58 years.

Born blind to the extent of not being able to see to read, but can see vaguely and sufficient to get about. Feels quite well. Used to get bad heads all her life, coming on in attacks lasting two to three days and leaving her "bewildered and heavy headed." No weakness in arms or legs. Hearing good. Never has fits or convulsions. Fainted many years ago. Putting on weight to a slight extent.

Past history.—No serious illness. Had eight children; seven are alive, two quite well, others affected. There were two miscarriages.

Present condition.—Intelligent well-covered woman of medium height. Hair of fine texture and moderately thin; sparsity of hair over halves of eyebrows.

Pupils.—Moderately dilated and react to both light and accommodation. Right divergent squint with weakness of right internal rectus. Lateral nystagmus with regular movements of medium nature; no vertical or rotatory nystagmus. High palatal arch; crowded irregular teeth, especially in lower jaw. No VII or V nerve paresis. There is flexion of wrist with hyper-extension of fingers—more marked on left. Fine tremor of fingers of outstretched hand. Hypotonus of both arms, left more than right. No weakness of grip or other motor functions of upper limbs. There is slight intention tremor of both hands, left more than right. Dysdokokinesia is present, slightly more in evidence on left side. Both hands show "crooking" of little fingers with concavity inwards, a small rudimentary nail on ulnar side of each index finger, deviation of terminal phalanx of each middle finger to the radial side. The index finger has limited movement at terminal phalanx and absence of skin ridges over upper halves. Both feet show rudimentary toe nails on outer aspect of first toe. Good motor power in all muscles of lower limbs. No inco-ordinations of lower limbs. Sensation to pin prick, cotton wool, position and stereognosis, all good.

Reflexes.—Deep reflexes of arms and legs are brisk; abdominal reflexes are all present; plantaris, both flexor. Rombergism absent. Gait normal. Peripheral arteries soft and of moderate tension. Blood pressure, 160/85; heart normal and regular, rate 72; lungs clear; abdomen clear; laboratory tests: Wassermann reaction negative; blood group II Moss; blood urea 34 mgms. per cent.; blood sugar 0.119 per cent.

(*b*) *Alfred,* aged 29 years.

Used to be a labourer. Not worked for three years on account of eyes. Born with impaired vision. Can just see to read with book on him; is able to get about quite well. Hearing good. Feels well otherwise. No headaches, fits, convulsions or fainting attacks.

Past history.—Operation—tracheotomy when a child.

Present condition.—Thin, spare muscular man of medium height. Tall oblong-shaped head. Pupils of medium size, react well to light, but sluggishly to accommodation. Divergent squint—left more than right. Rapid regular nystagmus on lateral fixation, left more than right. No ocular palsies. No VII or V nerve paresis. High narrow palatal arch. Lower jaw, teeth crowded. Soft palate and tongue show no palsies. Small old tracheotomy scar in neck. The little fingers of each hand are shortened by the presence of only two phalanges. Both index fingers have no proper nails; the right has slight rudimentary linear nail three inches long, the left has only two lateral linear depressions, but no nail. The right index finger is fixed and immobile at the proximal inter-phalangeal joint, the terminal phalanx bending dorsalwards only. Limitation of movement is present in the left index finger, but the finger is not completely fixed. Both index fingers are dwarfed and the skin folds are absent especially over joints. Both thumbs show a rudimentary supernumerary digit sprouting ulnarwards from the base of terminal phalanx. The right is larger than the left and neither has a nail bed. The terminal phalanx of each middle finger is held slightly flexed and deviated to radial side. Right foot: has four toes, the big toe is bulbous with no nail, but two small depressions on the tip; the first toe is longer than the rest and is held in hyper-extension. Left foot: has five toes, the 1st and 2nd are webbed up to the 1st phalanx. The big toe is bulbous, devoid of nail. The little toe is rudimentary and small and has no nail. The terminal phalanx of each big toe is held hyper-extended.

In both the upper and lower limbs.—No alteration in tone of muscles; no weakness of muscle power; no inco-ordination; no tremor in hands; no intention tremor. No dysdokokinesia. Sensation to cotton wool, pin prick, sense of position and stereognosis all good.

Reflexes.—Deep reflexes upper and lower limbs all good; abdominal reflexes all present; plantaris—not satisfactorily tested on account of hyper-extension of toes. No Rombergism. Gait good. Arteries soft and of medium tension. Blood pressure 125/75; heart, normal and regular; lungs, clear; abdomen, clear; both testes in scrotum. Laboratory tests: Wassermann reaction, negative; blood group, IV Moss; blood urea, 61 mgms. per cent.; blood sugar, 0.060 per cent.

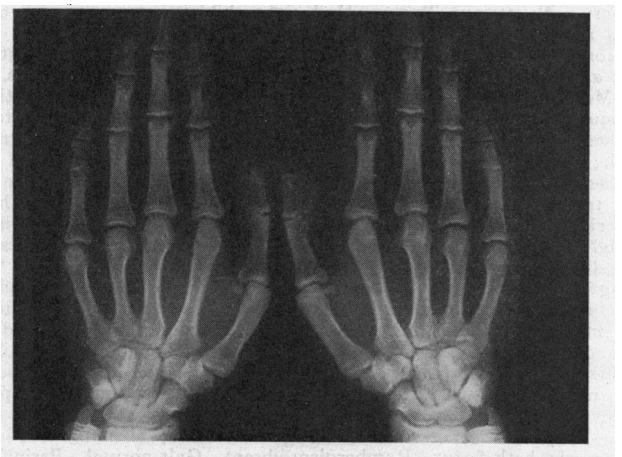

FIG. 13.

Hands of James.

Note.—(1) Deformity of little finger. (2) Stunting of 2nd phalanx and the atrophy of terminal phalanx of little finger.

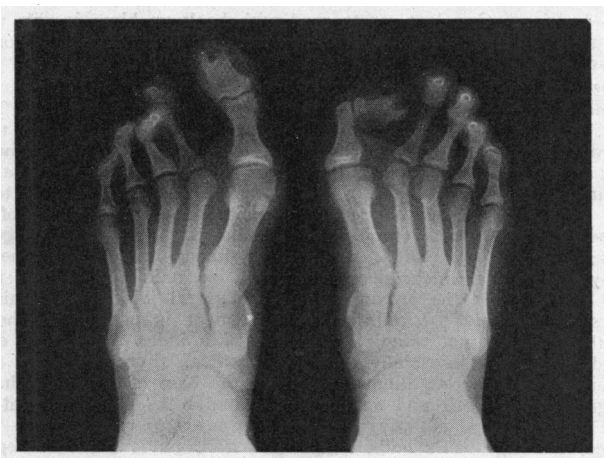

FIG. 14.

Feet of James.

Note.—(1) Bifidity of terminal phalanx of big toe with dislocation and atrophy of proximal phalanx of the big toe of the left foot. (2) Deformity of other toes and changes in the terminal phalanges.

(*c*) *James,* aged 16 years. No occupation.

Born with impaired vision of both eyes, but he can see to read. Hearing good up to three years ago, when he had bilateral mastoidectomy. Hearing poor since then. Feels well otherwise. No weakness of limbs. No headaches, never fits, convulsions or fainting attacks.

Present condition.—A tall, well-developed youth of good intelligence; very deaf. Bilateral mastoid scars. Tall oblonged head. Pupils of medium size; sluggish reaction to light, poor reaction to accommodation. Bilateral divergent squint. Coarse irregular nystagmus to right and left without lateral fixation. No VII or V

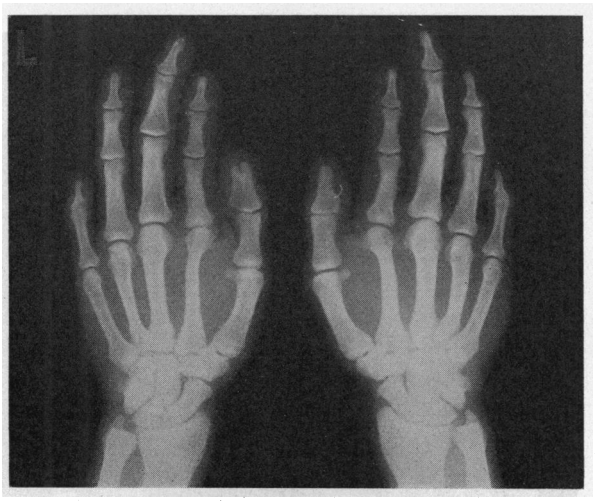

FIG. 15.

Hands of Charles.

Note.—(1) Bifid terminal phalanx of left hand. (2) Suppression of 2nd phalanx of little finger.

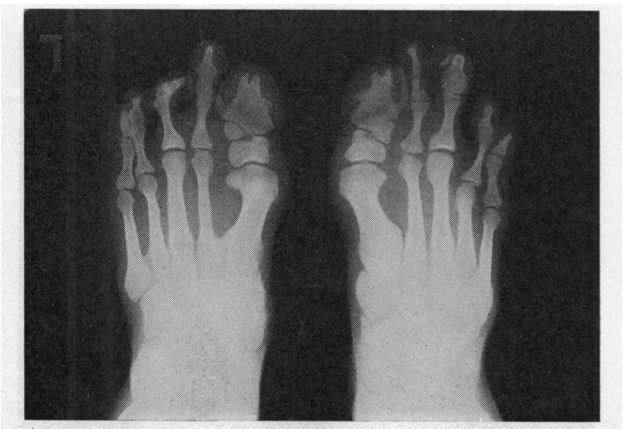

FIG. 16.

Feet of Charles.

Note.—(1) Bifidity and other deformities of terminal phalanx of big toe. (2) Presence of an accessory bone between the two phalanges of the big toe. (3) Atrophic appearance of the 2nd and 3rd phalanges of the other toes.

nerve palsy. Tongue and palate, no paresis. High narrow palatal arch—teeth somewhat crowded, especially in lower jaw. Very fine tremor of outstretched fingers. No abnormality of tone. Good motor power in muscles of hands and arms. Good power in muscles of legs. No inco-ordination upper or lower limbs. No dysdokokinesia. No intention tremor.

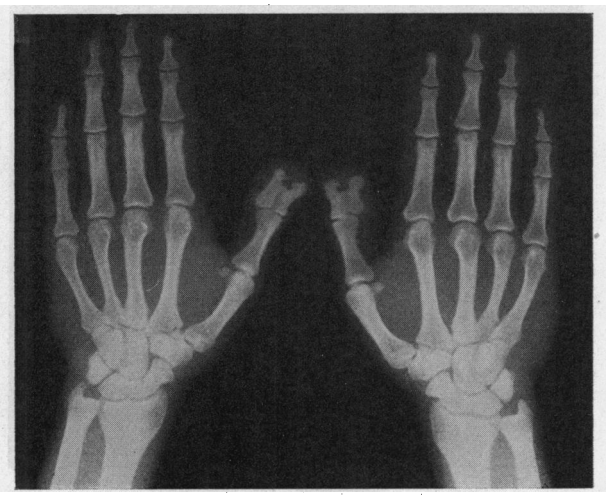

FIG 17.

Hands of Edward.

Note.—(1) Bifidity of terminal phalanx of thumbs. (2) The stump-like appearance of the thumbs.

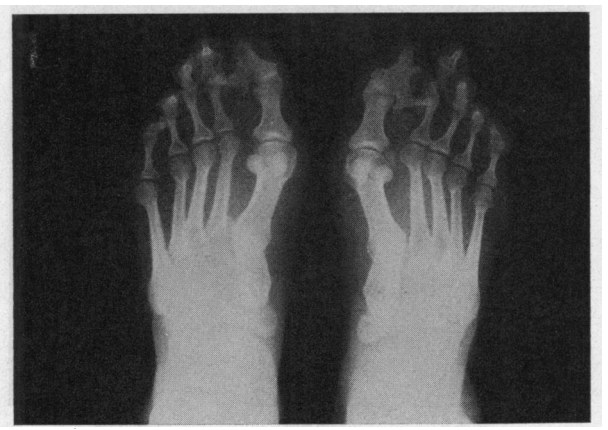

FIG. 18.

Feet of Edward.

Note.—(1) Bifidity and other deformities of terminal phalanx of big toe. (2) Atrophic appearance of the terminal phalanges of the other toes.

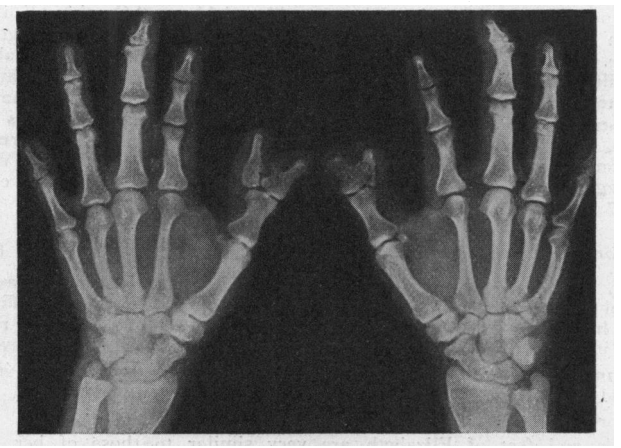

FIG. 19.

Hands of Alfred.

Note.—(1) Complete bifurcation of terminal phalanx of left thumb and partial bifurcation of the corresponding phalanx of the right thumb. (2) Stunting of the little finger with suppression of the 2nd phalanx.

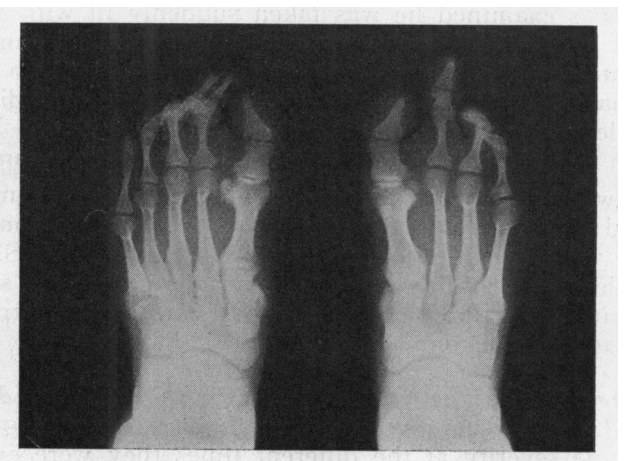

FIG. 20.

Feet of Alfred.

Note.—(1) Absence of bifurcation with atrophy of the terminal phalanx of big toe. (2) Complete suppression of the 5th toe of the right foot. (3) Abnormal appearance of 2nd and 3rd phalanges of little toe of the left foot. (4) Abnormal appearance of the other terminal phalanges.

Reflexes.—Deep reflexes upper and lower limbs all brisk; plantaris, flexor; abdominal reflexes all present. Sensation to pin prick, cotton wool, sense of position and stereognosis all good. Skin of hands cold and blue. "Crooking" of both little fingers with convexity outwards. Rudimentary nails on both index fingers—smaller on left side. Skin over terminal phalanx of left index finger shows absent folds. Marked hallux valgus on right side. Both big toes broad, the left having a split nail; first toe on each foot has bulbous terminal, with rudimentary nail on each. First and second toes of each foot webbed to first phalanx. Arteries soft, pulse regular, 78, somewhat collapsing. Blood pressure, 130/30; heart, normal; lungs, clear; abdomen, clear; both testes in scrotum. Laboratory tests: Wassermann reaction, negative; blood group, II Moss; blood urea, 29 mgms. per cent.; blood sugar, 0.077 per cent.

(*d*) *History and condition of the three other affected members of the family*:

Elizabeth, the eldest, has worked as a laundress at a hospital since leaving school. Her general health is good, and her vision, though poor, is not sufficiently bad to prevent her from doing her work. The Matron of the hospital reports that Elizabeth's vision is probably poorer than she would lead people to believe.

Edward and Charles are in in good health and have been employed in a factory for the blind since leaving school.

All the three are of medium stature.

The hands and feet of Elizabeth are very similar to those of her mother, so much so that the description given of the external appearance of the mother's limbs holds good for the daughter. The external appearances of the hands and feet of Edward and Charles reveal greater deformity, and correspond to the appearances shown radiographically. Nails are absent on the index fingers and big toes in all the three, only rudimentary nails in the form of two lateral grooves being present. The macular colobomata in Elizabeth (not pictured) are very similar to those in her mother.

5. *Solitary kidney in one of the patients.*—Three months after Edward was examined he was taken suddenly ill with influenza and died within 24 hours from purulent pericarditis and apical consolidation of the lungs, established post-mortem. In addition to the characteristic pathological findings, it was also discovered that the left kidney and suprarenal gland were absent. Unfortunately an eye could not be obtained for histological examination.

In view of the renal abnormality, Mrs. S. and James were submitted to uroselectan examination, but no renal abnormality could be found. Injection of uroselectan into Mrs. S. proved impossible by the ordinary methods on account of the smallness of her veins; injection had to be made after surgical exposure of the median cephalic vein.

6. *The functional activity of the eyes in the mother and affected sons.*—All the patients reveal horizontal pendulum nystagmus, not of the same severity at the different times they were examined. There are no subjective sensations associated with it. There is no night-blindness; light sense and colour vision are good. The fields are full in the four sons, but in the case of the mother there is a large nasal defect hemianopic in extent in the right eye. There is no scotoma corresponding to the coloboma.

Refraction:

Mrs. S.	R.	−3·0	D. sph.	c̄	−2·0	D. cyl.	axis 45°
	L.	−2·0	„	„	−1·5	„	„ 135°
Alfred	R.	−3·0	„	„	−4·0	„	„ 45°
	L.	−3·0	„	„	−4·0	„	„ 135°
Edward	R.	−2·0	„	„	−1·5	„	„ 45°
	L.	−2·0	„	„	−1·5	„	„ 135°
Charles	R.				−3·0	„	„ 30°
	L.	−1·0					
James	R.				−2·5	„	„ 45°
	L.				−4·0	„	„ 140°

Vision in all these patients is in the neighbourhood of 3/60 with correction.

Elizabeth's refraction and fields were not determined.

III.—Discussion

1. *The skeletal abnormality. Relationship to apical dystrophy of hands and feet.*—Under the term apical dystrophy, MacArthur and McCullough have isolated a rare entity from out of the mass of hereditary defects grouped under the term brachyphalangy. The essential features in their own cases and in the nine other groups they have collected from the literature are the following:—

(1) Whilst the fingers are short, there is no reduction or peculiarity in the metacarpals (or metatarsals) or in the epiphysis or shaft of the proximal phalanx. Abnormalities are confined to the two outer phalanges, whose bony elements undergo reduction much more marked than those of fleshy parts or nails.

(2) In general, in fingers and toes that are much shortened the distal (third) phalanx is entirely omitted, and the second is represented by a small rounded (epiphyseal) remnant or by a more developed structure.

(3) Associated characteristics.

(*a*) Syndactyly of the fleshy structures in both hands and feet is occasionally present.

(*b*) Doubling of thumbs. The thumbs tend in all cases to be abnormally stout and particularly broad and thinned at the tip, and possess wide, thin, brittle and very slowly growing nails. The nails are often split partly or wholly in two. The splitting of the bone is more or less obvious in all the thumbs radiographed, and would seem to be a regular, though variable, feature of the affection.

The abnormality is inherited in manner of a simple Mendelian dominant. In contrast to the classical type of brachyphalangy, the deformity is present at birth, the brunt of the shortening of digits does not fall on the second phalanx, stature is not affected,

and the disturbance, instead of being a localized interference with the growth of bone, is probably an embryonic failure of development of the tip of the digit.

Though showing some departure from the features recorded by MacArthur and McCullough the skeletal deformity in our patients conforms, in the main, to type. The absence of any defect in the metacarpals and metatarsals as also in the first phalanges is constant, and of the defect in the second and terminal phalanx, the brunt is in most cases on the third phalanx. Doubling of thumbs is practically present throughout the series, if the mother is excluded, and in her case the terminal phalanx is rather bulbous.

2. *The association of skeletal, ocular and kidney defects in experimental embryology.*—From his studies on the creeper fowl, a breed characterized by extreme shortness of the long bones of the extremities with bending of the tibia and the presence of a highly differentiated fibula, Landauer has shown that the condition is dominant and when homozygous is lethal, death coming on at about 72 hours of embryonic life. Ophthalmologically his investigations are of interest as, in addition to the skeletal deformity, ocular defects are present in those exceptional cases of homozygous embryos that have survived for more than 72 hours. In such the lids are rudimentary, the globes hardly developed, the scleral cartilage missing whilst the rest of the sclera is thin; and with but few exceptions there is a coloboma near the entry of the optic nerve.

What looks like the experimental production of a triad of deformities is described by Bagg and Little and their collaborators (Bean, Little and McPheters). In 1924 Bagg and Little reported deformities in the third generation of mice which had been exposed experimentally to X-radiation. These deformities implicated (1) the eye and fore-face; (2) foot and leg; (3) the length and colour of hair over a saddle area; and (4) the jaw. The jaw deformity was regarded as being inherent in the breed and not the result of the radiation.

These mice have now been bred over a large number of generations and many hundreds in number.

During the course of these investigations it was found that visceral abnormalities were also present—mainly defects of the kidney, varying from complete atrophy of one kidney, the congenital solitary kidney condition, to the complete absence of both kidneys. In a series of 1,817 autopsies it was found that blindness and various defects of the limbs—syndactylism, polydactylism and especially club foot— are closely in association with renal abnormality. The visceral abnormality, like the eye and foot abnormality, is recessive.

The eye abnormality has a wide range, involving abnormality

of the lids from slight atrophy to complete absence, or of the globe itself from slight atrophy with or without corneal opacity to marked atrophy of the globe with clear cornea. The changes in the limbs are also of a widely varying character; from club foot with dorsal or with palmar flexion with or without distortion of the entire foot, to more localized lesions such syndactylism, hypodactily and polydactily.

From an examination of over 5,200 individuals, descendants to the nineteenth generation, abnormal development seems to resolve itself essentially to the triad of eye defect, kidney defect and limb defect, whilst a detailed analysis shows that "a tendency to eye defects and the loss of one or both kidneys is associated with polydactylism" (Bagg, 1929). This polydactyly includes bifid first toes.

The causal origin of these defects is held by Bagg to be extensive haemorrhagic lesions present in the latter part of pregnancy. These haemorrhagic lesions have been found over the site of the abnormally developing eye and on the abnormally developing limbs. The haemorrhagic area develops from lymph stasis leading to a "well defined bleb, or blister-like area . . . filled with a clear amber-coloured fluid. The next step . . . is the escape of blood into the bleb, and in consequence, the formation of a well-defined haemorrhagic lesion" (Bagg, 1929). Bonnevie extended these investigations and holds that cerebro-spinal fluid and not lymph is the original fluid in the blebs and that a primary excess of cerebro-spinal fluid is distributed into different areas of the body by mechanical forces— a thesis worked out with great detail and of great value in explaining the distribution of defects.

3. *Macular coloboma as localized choroideremia.*—This conception borrowed from Treacher Collins though it does not help to explain most of the essential features of macular coloboma—such as the presence or absence of pigment, to mention only one—is of value not only because it represents an actual ophthalmoscopic observation, but also for the reason that it helps to link central colobomata with colobomata situated elsewhere outside the choroidal cleft. Furthermore, the absence of a scotoma in some of the cases of macular coloboma is best explained by invoking a lesion which affects the retina only secondarily and to a variable degree. What evidence there is anatomically is also in favour, as far as it goes, of a primary choroidal affection.

The presence of skeletal defect in cases of coloboma would also seem to point to the primary lesion being mesodermal in site rather than ectodermal, but it is possible to argue that the lesions are embryologically unrelated and linked by inheritance. Moreover, even if the macular coloboma is mesodermal in origin it does not follow that the blood supply is at fault.

The view that macular colobomata are the result of defective localized vascularization gains some support from the cases of familial central choroidal angio-sclerosis to be published in a forthcoming paper in this Journal. The sharply-circumscribed central area with its non-effective underlying choroidal vessels rather suggest that these cases of choroidal sclerosis are allied to macular coloboma—coloboma on the one hand and "senile" macular degeneration due to choroidal sclerosis on the other, representing the two extremes of a continuous range of dystrophy in which the three cases of choroidal sclerosis with onset in early life form a connecting link.

Summary

1. The literature on congenital macular coloboma is reviewed, and from the sifted material, 20 cases of bilateral macular coloboma, 36 unilateral and three (possibly five) familial groups, are considered. There is nothing in the ophthalmoscopic appearances of the lesion which stamps any particular defect as definitely congenital, as opposed to lesions of post-natal origin.

2. Attention is drawn to cases in which macular coloboma was present in the same eye together with a typical choroidal coloboma, as also to cases in which macular coloboma was associated with other atypical colobomatous defects.

3. One suggestion that emerges is that non-pigmented colobomata tend to be deeply excavated whilst excavation in pigmented colobomata is relatively less marked.

4. It would appear that in addition to the recognized varieties of non-pigmented and pigmented macular coloboma, a third type, aptly described as a wheel-figure, has a fairly characteristic appearance. In this type the centre is white and from it pigmented spokes radiate towards a pigmented rim.

5. Studies in the pathological anatomy of macular coloboma, though none of them conclusive, would appear to indicate that there is no basis for the belief that congenital macular colobomata are the result of intra-uterine inflammation.

6. A description is given of a familial group consisting of a mother and five children, all of whom showed bilateral pigmented macular coloboma. Associated with this defect was a rare skeletal abnormality known as apical dystrophy of hands and feet. In one of the patients, the condition of solitary kidney was present.

7. Attention is drawn to the studies of Landauer on the creeper fowl, a breed characterized by skeletal defects and ocular abnormalities. Consideration is also given to the work by Bagg

and Little and their collaborators on the experimental production of hereditary defects in mice, the defects involving the eye, feet and kidney.

8. Arguments are advanced in favour of regarding macular coloboma as a localized choroideremia.

I have to acknowledge the helpful criticisms of Dr. E. A. Cockayne, Mr. A. D. Griffith, Mr. T. W. Letchworth and Mr. A. H. Levy. To Dr. David Krestin I am indebted for the general examination of the patients described, and to Mr. J. R. M. Wigham, Medical Superintendant, St. Andrew's Hospital, for the post-mortem report discussed. To the *Brit. Jl. of Ophthal.* I am indebted for a grant to cover expenses.

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	Vol.	Page	Year
AGASTON.—*Arch. of Ophthal.*	48	377	1919
APPLEMAN.—*Amer. Jl. Ophthal.*	3	296	1920
CAR.—*Zeitschr. f. Augenheilk.*	57	618	1925
CLARKE.—*Brit. Jl. of Ophthal.*	11	97	1927
DOLLFUS.—*Bull. d'Ophtal.* Paris	—	442	1930
FEILCHENFELD.—*Centralbl. f. Prak. Augenheilk.* ...	35	68	1911
FISCHER.—*Ann. of Ophthal.*	15	1	1906
HANSELL.—*Trans. Amer. Ophthal. Soc.*	12	249	1909
HOEG.—*Acta Ophthal.*	5	199	1927
JOHNSON.—*Arch. of Ophthal.* (Cases 11-12)	19	1	1890
KASTALSKY.—*Arch. f. Augenheilk.*	36	59	1898
KIMPEL.—*Arch. f. Augenheilk.*	37	45	1898
LEMKE.—Das Kolobom der Macula lutea. Thesis. Rostock, 1913.			
OELLER.—Atlas seltener ophthalmoskopische Befunde. Part III, E. Table IV. Wiesbaden, 1904.			
PEIRCE.—*Amer. Jl. Ophthal.*	15	53	1932
PRZYBLYSKA.—*Ann. d'Ocul.*	163	367	1926
SCHMIDT-RIMPLER.—*Arch. f. Ophthal.*	26	221	1880
SEEFELDER.—*Kurzes Handb. der Ophthal.* Berlin, Bd. I, S. 537, 1930.			
SHOJI.—*Arch. d'Ophtal.*	43	21	1926
VAN DER HOEVE.—*Arch. f. Augenheilk.*	46	66	1903
WEEKS.—*Arch. of Ophthal*	47	307	1918

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	Vol.	Page	Year
DEBIERRE.—Given by Picque, p. 259. (See ref. under Discarded cases.)			
DUTOIT.—*Arch. f. Augenheilk.*	69	127	1911
GENET.—*Lyon Medical*	129	277	1920
GOULDEN, given by CLARKE, *Brit. Jl. of Ophthal.* ...	11	97	1927
HEPBURN.—*Proc. Roy. Soc. Med.*, Vol. 14, Part III, Sect. Ophthal., 26, 1920-1.			
HIRSCHBERG.—*Arch. f. Ophthal.*	21	178	1875
HORTON.—*Amer. Jl. of Ophthal.*	9	196	1926
HUNNEMAN.—*Amer. Jl. of Ophthal.*	5	727	1922
KRAWTSCHENKO.—Ref. *Nagel's Jahresber.*	—	242	1896
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LEWIS.—*Amer. Jl. of Ophthal.*	11	992	1928
LISTER.—*Trans. Ophthal. Soc. U.K.*	20	188	1900
MENACHO.—Ref. *Klin. Monatsbl. f. Augenheilk.* ...	57	410	1916
MEYER.—*Rev. gen. d'Ophtal.*	3	155	1884
Ibid.	4	155	1885
OELLER.—Ophthalmoskopisches Atlas. Abtheil. E. Table III. Wiesbaden, 1899.			
POLJAK.—*Zeitschr. f. Augenheilk.*	63	285	1927
PREOBRASCHENSKY.—*Zeitschr. f. Augenheilk.*	31	454	1913
REISS.—*Klin. Monatsbl. f. Augenheilk.*	40 ii	395	1903
REMAK.—*Centralbl. f. Prak. Augenheilk.*	8	275	1884
RUMSZEWICZ.—*Rev. gen. d'Ophtal.*	4	152	1885
SCHNABEL.—*Wien. med. Blätter*, No. 6 and seq. (Case 2)	—	—	1884
SCHWEIGGER—*Handb. der Augenheilk.*, 1e Aufl.	—	36	1872
SILCOCK.—*Trans. Ophthal. Soc. U.K.*	20	188	1900
SILEX.—*Arch. f. Augenheilk.*	18	289	1888
Also in *Arch. of Ophthal.*	18	86	1888
SOKOLOW.—Ref. *Zeitschr. f. Augenheilk.*	27	378	1912
STREATFEILD.—*Ophthal. Hosp. Repts.*	5	79	1866
TARNAWSKY.—Ref. *Zeitschr. f. Augenheilk.*	5	479	1901
VAN DUYSE.—*Ann. d'Ocul.*	98	108	1887
VON HIPPEL.—Graefe-Saemisch, 2te Aufl., Band 2, Abt. 1, Kap. 9, S. 24, 1908.			
DE WECKER.—*Handb. der ges. Augenheilk.* (Graefe-Saemisch, 1e Aufl., iv, 595, 1876).			
DE WECKER et DE JAEGER.—Traité des maladies du fond de l'oeil et atlas d'ophtalmoscopie. Paris, 1870, p. 207.			
WOOD.—*Trans. Ophthal. Soc. U.K.*	12	173	1892

FAMILIAL MACULAR COLOBOMA

	Vol.	Page	Year
BLANK.—*Zeitschr. f. Augenheilk.*	64	388	1928
CLAUSEN.—*Klin. Monatsbl. f. Augenheilk.*	67	116	1921
Ibid.	81	385	1928
Zeitschr. f. Augenheilk.	66	253	1928
DAVENPORT.—*Proc. Roy. Soc. Med.*	21	109	1927
LEONARDI.—Ref. *Centralbl. f. Ophthal.*	22	649	1929-30
SCHOTT.—*Klin. Monatsbl. f. Augenheilk.*	67	415	1921

DISCARDED CASES

	Vol.	Page	Year
BATTEN.—*Trans. Ophthal. Soc. U.K.*	32	133	1912
BIRNBACHER.—*Arch. f Augenheilk.*	15	159	1885
BOCK.—Die Angeborenen Kolobome des Augapfels. Vienna, 1893. (Cases LI and LII.)			
BURNETT.—*Arch. of Ophthal.*	11	460	1882
*COLLINS.—*Proc. Roy. Soc. Med.*	21	109	1927
COSMETATOS.—*Zeitschr. f. Augenheilk.*	14	575	1905
CRAMPTON.—*Tr. Coll. Phys.*, Phil.	37	394	1915
*DAMEL and VENTOLA.—Ref. *Centralbl. f. gesam. Ophthal.*	26	265	1931
*DAMOS.—*Centralbl. f. gesam. Ophthal.*	18	653	1927
*DAVENPORT —*Proc. Roy. Soc. Med.*	20	436	1926
DEYL.—*Wien. Kl. Rundschr.*	13	17	1899
XII Int. Med. Cong. Med. Moscow	11	261	1897
DICKS and SAWHNEY.—*Brit. Jl. of Ophthal.*	13	445	1929

*Not reported in full or not available in original.

	VOL.	PAGE	YEAR
DOR.—*Rev. gen. d'Ophtal.*	7	312	1888
DUANE.—*Arch. of Ophthal.*	32	319	1903
FROST.—Fundus Oculi. Edin. and London, 1896. Plate XXII. Figures 51 and 52. P. 102.			
FUCHS.—*Arch. f. Ophthal.*	23	155	1882
*GUEDES DE MELLO.—*Brazil-med.*	12	220	1898
HAAB.—Atlas. of Ophthalmoscopy, English Edition, London, 1928. Fig. 8*b*.			
*HELMICH.—Thesis. München, 1920.			
*HOEG.—*Acta Ophthal.* (Cases 1, 2 and 4)	5	199	1927
JODKO.—Quoted in *Nagel's Jahresber.*	7	218	1876
JOHNSON.—*Arch. of Ophthal.* (Cases 4, 5, 8, 9 and 10)	19	1	1898
KANZEL.—Ref. *Zeitschr. f. Augenheilk.*	19	361	1900
KASAS.—Ref. *Zeitschr. f. Augenheilk.*	18	—	1907
*KATZNELSON.—Ref. *Centralbl. f. gesam. Ophthal.* ...	19	605	1927
*KNORR.—*Amer. Jl. of Ophthal.*	6	507	1923
*KRACHMALNIKOW.—Ref. *Centralbl. f. gesam. Ophthal.*	24	685	1930
LAPERSONNE, DE.—*Arch. d'Ophtal.*	8	118	1888
LEDERKARL.—*Acta Ophthal.* (Cases 1 and 3)	12	255	1934
MONPROFIT.—*Arch. d'Ophtal.*	5	139	1895
MONTMEJA.—*Rev. photograph. des hopitaux de Paris* ...	4	48	1872
*NICHELATTI—.Ref. *Klin. Monatsbl. f. Augenheilk.* ...	70	548	1923
NUEL.—*Ann. d'Ocul.*	93	174	1885
OELLER.—Ophthalmoskopisches Atlas. Abtheilung E. Table IV. Wiesbaden, 1899.			
*OSTRONMOW.—Ref. *Zeitschr. f. Augenheilk.*	27	282	1912
PICQUE.—Anomalies de developpement et maladies congénitales du globe de l'oeil. Thesis. Paris, 1886. P. 235.			
*RABINOWITCH.—Ref. *Ergebn. allgem. Path. Ergänzungsband* 1	21	536	1927
REICH.—*Klin. Monatsbl. f. Augenheilk.*	10	56	1872
*RISLEY.—*New York Med. Jl.*	42	134	1885
SCHNABEL.—*Wien. Med. Wochenschr.*	—	832	1876
Wien. Med. Blätter, Nos. 6, 8 and 9. 1884. (Cases 1, 3 and 4.)			
*SMIRNOW.—Ref. *Zeitschr. f. Augenheilk.*	22	551	1909
*TSCHEMOLOSOFF.—Ref. *Zeitschr. f. Augenheilk.* ...	12	797	1904
TALKO.—*Klin. Monatsbl. f. Angenheilk.*	8	165	1870
VAN DUYSE.—*Ann. d'Ocul.*	91	1	1884
Ibid.	96	139	1886
*WATSON.—*Amer. Jl. of Ophthal.*	8	226	1925
WIETHE.—*Arch. f. Augenheilk.*	14	11	1885
WOOTTON.—*Arch. of Ophthal.*	40	292	1911
*ZIRKULENKO.—Ref. *Ergebn. allgem. Path. Ergänzungsband* 1	21	536	1927

* Not reported in full or not available in original.

OTHER REFERENCES

	VOL.	PAGE	YEAR
BAGG.—*Amer. Jl. Anat.*	36	275	1925–6
Ibid, ...	43	167	1929
Ibid.	33	119	1924
BAGG and LITTLE.—*Jl. Exper. Zool.*	41	45	1924–5
BEAN.—*Amer. Jl. Anat.*	43	221	1929
BEAUMONT.—*Trans. Ophthal. Soc. U.K.*	11	221	1891
BOCK.—Die Angeborenen Kolobome des Augapfels. Vienna, 1893. (Cases VII and VIII.)			
BONNEVIE.—Arhandlinger det Norske Videnskaps Akademic Oslo. I Mat-Naturv. Klasse No. 13. 1930. (In German.)			

	Vol.	Page	Year
BUTLER.—*Proc. Roy. Soc. Med.*	20	439	1926
Ophthalmoscope	8	409	1910
CLAUSEN.—*Klin. Monatsbl. f. Augenheilk.*	67	116	1921
Ibid.	81	385	1928
Zeitschr. f. Augenheilk.	66	253	1928
COLLINS.—*Proc. Roy. Soc. Med.*	20	437	1926
COLLINS and MAYOU.—Pathology and Bacteriology of the Eye. Second Edition, p. 106. London, 1926.			
DAVENPORT.—*Proc. Roy. Soc. Med.*	20	436	1926
DEUTSCHMANN.—*Arch. f. Ophthal.*	102	1	1920
DEYL.—*Wien. Kl. Rundschr.*	13	17	1899
XII Int. Med. Cong. Med. Moscow	11	261	1897
FORSMARK.—Svenska Lakaresallskapet Handlingar ...	42	442	1916
FUNCCIUS. Das sogenannte Colobom der Macula lutea. Thesis. Tübingen, 1913.			
HESS.—*Arch. f. Ophthal.*	36	136	1890
HIRSCHBERG.—*Arch. f. Ophthal.*	21	178	1875
HOEG.—*Acta Ophthal.* (Cases 1, 2 and 4)	5	199	1927
JANKU.—Quoted by Seefelder in *Ergebnisse allgem. Pathol. Ergänzungsband I.*	21	537	1927
JOHNSON.—*Arch. of Ophthal.* (Case 6-7)	19	1	1890
KASTALSKY.—*Arch. f. Augenheilk.*	36	59	1898
KIMPEL.—*Arch. f. Augehheilk.*	37	45	1898
LAGRANGE.—*Arch. d'Ophtal.*	43	65	1926
LANDAUER.—*Arch. f. Ophthal.*	129	269	1932
LANDAUER and DUNN.—*Jl. of Genetics*	23	397	1930
LEDERKARL.—*Acta Ophthal.* (Cases 1 and 3)	12	255	1934
LITTLE and MCPHETERS.—*Jl. of Genetics*	17	674	1932
MACARTHUR and MCCULLOUGH.—*Human Biology* ...	4	179	1934
MANN.—*Brit. Jl. of Ophthal.*	11	99	1927
Proc. Roy. Soc. Med.	20	434	1926
MEISNER.—*Zeitschr. f. Augenheilk.*	73	333	1931
MENACHO.—Ref. *Klin. Monatsbl. f. Augenheilk.*	57	410	1916
MICHAELSON.—*Centralbl. f. Prak. Augenheilk.*	13	108	1889
PARSONS.—The Pathology of the Eye, pp. 828 and 845. London, 1906.			
PARSONS and COATS. *Brain*	29	209	1906
REICH.—*Klin. Monatsbl. f. Augenheilk.*	10	56	1872
Ibid.		270	
RONES.—*Amer. Jl. Ophthal.*	17	883	1934
RÖSSLER.—*Arch. f. Ophthal.*	80	296	1912
SCHMIDT-RIMPLER.—*Arch. f. Ophthal.*	26	221	1880
——— *Deut. med. Woch.*, Vol. 25, 1899; Vereinsbeilage, p. 144.			
SCHOTT.—*Klin. Monatsbl. f. Augenheilk.*	67	415	1921
SOCOLOVA.—Ref. *Arch. of Ophthal.*	7	308	1932
SORSBY.—*Brit. Jl. of Ophthal.* (Case 5)	15	1	1931
STREATFEILD.—*Ophthal. Hosp. Repts.*	5	79	1866
VAN DUYSE.—*Arch. d'Ophtal.*	19	25	1899
VAN LINT.—*Bull. Soc. Belge d'Ophtal.*, Nos. 37 and 38 ...	—	10	1914
VON AMMON.—*Munch. illus. med. Zeitschr.*, 1852. Quoted by Bock.			
WECKER, DE.—*Hanb. der ges. Augenheilk.* (Graefe-Saemisch, 1e Auf., 1876)	4	595	—
Klin. Monatsbl. f. Angenheilk.	10	176	1870
WIETHE.—*Arch. f. Augenheilk.*	14	11	1885
WÜRDEMANN.—Injuries of the Eye. Second Edition. Plate VIII. London, 1932.			
ZIMMERMANN.—*Klin. Monatsbl. f. Augenheilk.*	35	226	1897