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COMMUNICATIONS

CHOROIDO-RETINAL DYSTROPHY*

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A FAMILY is described with unusual fundus lesions not readily classified in any of the recognized types. The family is of further interest in that, though the affection is clearly hereditary, the mode of inheritence is of considerable complexity.

The M family (Fig. 1) is descended from a man who is known to have been blind but who died in 1950. His wife, also deceased, is reputed to have had normal sight. He had three sons (II, 2, 7, 10) who were normal; two of them have had normal children, the other being unmarried. He also had seven daughters, all of whom have had sons (numbering ten altogether) affected by a choroido-retinal disease accompanied by myopia.

The earliest symptom of this disease is night blindness and the earliest fundus change is exposure of the choroidal vessels, which has been observed at the age of 2 years. The disease is steadily progressive; before their teens the boys have had to be sent to a Blind School, and by the age of 20 they are certifiably blind though they may be able to work in appropriate occupations. The eldest in this family, aged 32, has only perception of hand movements.

Of the seven proven carrier women in generation II, four are apparently completely normal but three (II, 1, 3, 6) show anomalous fundus appearances with varying degrees of visual defect, the earliest symptoms having been noticed at the age of 20 or later. In only one (II, 6) has the condition progressed to certifiable blindness and she is the only one who is myopic.

General Aspects.—There is no consanguinity in this family, except that one carrier daughter (II, 3) married a cousin on her mother's side. One girl (III, 19) is a high-grade mental defective, but all the others show normal intelligence. The blood Wassermann reaction was carried out on a number of the affected patients and was negative in each case.

There would appear to be overwhelming evidence that this disease is hereditarily determined and that it should be classified as an abiotrophy or heredo-degenerative disease. In many cases the onset is so early that it could be assumed that the disease is present at birth. However, it is clearly progressive and shows polymorphic appearances in different individuals, especially as between the sexes. It

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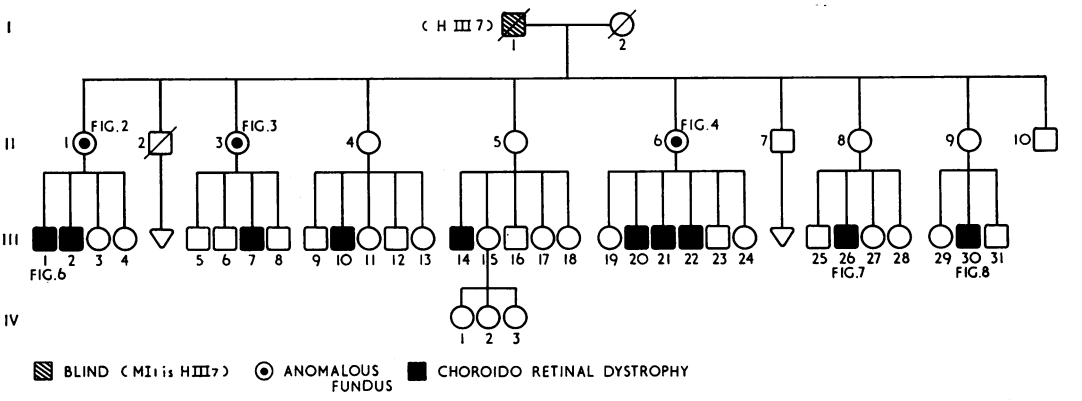

FIG. 1.—Pedigree of Family M.

would, therefore, appear better not to classify this as a congenital disease but to regard it as an abiotrophy of early onset. Its inheritance pattern clearly shows sex-linkage.

Condition in Affected Males.—This follows a fairly uniform pattern. The individual cases are reported in detail in the Appendix. Night blindness is observed in childhood, sometimes as early as the age of 3 years; the parents note a striking difference in the behaviour patterns of the affected sons compared with the normal, and all affected males are myopic. The youngest to be examined shows a fundus picture similar to that described in early choroideremia. By the time visual acuity can be assessed it is considerably reduced, and there is pigmentation of the bone corpuscle type and exposure of the choroidal vessels. The visual fields become contracted but no annular scotoma has yet been demonstrated. There is total colour blindness by the Ishihara tests. The older affected men have vision reduced to counting fingers or less. There is nystagmus, slight cataract, and pale fundi with scattered pigmentation, some of the bone corpuscle type.

Condition in Carrier Females.—Generation II includes seven sisters who are all proven carriers. Four of them (II, 4, 5, 8, 9) show absolutely normal fundi and normal vision; they are either emmetropic or have insignificant refractive errors. These women were examined for tapetal reflex which is not present.

The two eldest daughters (II, 1, 3: Figs 2 and 3) have fairly good vision though they say that they need stronger glasses than they used to, but their fundi show quite marked pigmentary changes of a type sometimes referred to as atypical retinitis pigmentosa. The pigmentation in these cases is much heavier than the bone corpuscle pigmentation seen in the affected males. There is also choroidal sclerosis but the retinal arteries are not markedly narrow. The discs are rather pale. The fifth daughter (II, 6: Fig. 4) is highly myopic; one eye only has counting fingers and the other 1/60 with correction. She first noticed her visual defect at the age of 20. She is now 40 and there seems no doubt that in her the condition is a progressive one.

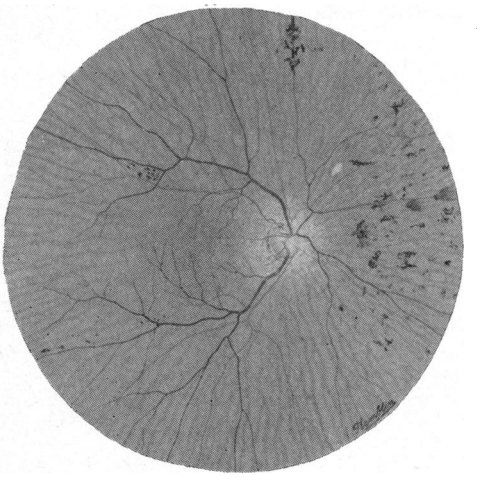

FIG. 2.—Fundus appearance II. 1.

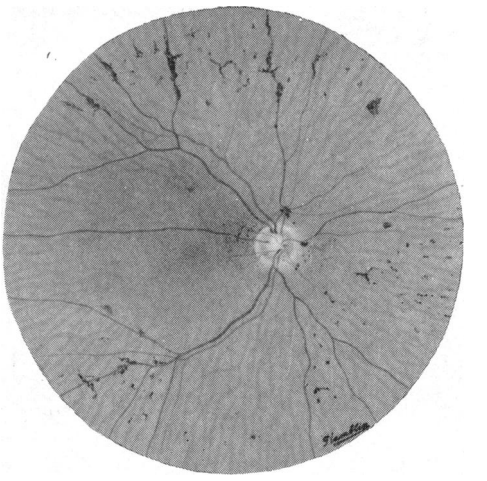

FIG. 3.—Fundus appearance II. 3.

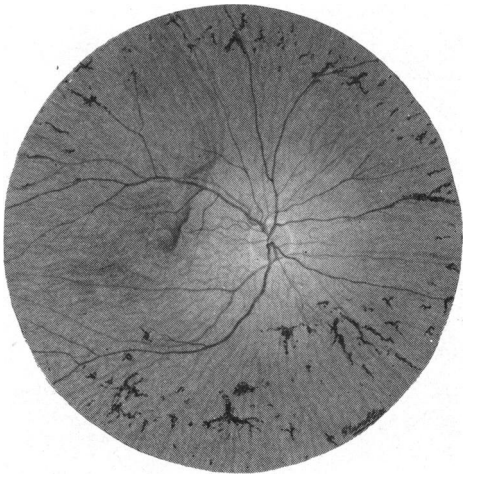

FIG. 4.—Fundus appearance II. 6.

Figs. 2—4 represent females of M family.

Females of the Third Generation.—All the females of the third generation have been examined. One (III, 19) is a high grade mental defective but all the other members of the family appear to be intelligent. Some of them showed a minimal tapetal reflex as may be seen in normal individuals. The oldest female in the third generation (III, 15), who is 23, is married and has three young daughters (IV, 1, 2, 3), all apparently normal.

All these females and their unaffected brothers are emmetropic with normal vision and visual fields and normal colour sense.

Refractive State.—In this family all the affected males are myopic, and all the unaffected males are emmetropic. All the female carriers are emmetropic with the exception of II, 6, the most severely affected of the carrier females who noticed a defect when she was 20. The other two female carriers with anomalous fundus

appearances (II, 1, 3) did not become aware of any defect of vision until middle life and in them there is no significant error of refraction.

All the females of the third generation, some of whom are probably carriers, have been found to be emmetropic or hypermetropic. It is quite clear that in the affected males the degenerative changes begin during childhood and progress throughout the period of growth. The occurrence of myopia in these males is possibly a secondary effect of the choroido-retinal dystrophy.

Amongst the carrier females one is led to suppose that the effect of the abnormal gene causing choroido-retinal dystrophy is neutralized by its allele on the normal X-chromosome, but that the neutralizing effect wears off and choroido-retinal dystrophy may occur at a later age. In the case of the severely affected carrier female (II, 6), it may be supposed that the neutralizing effect of the normal X-chromosome failed during the period of growth so that myopia developed, whereas in the two less affected carrier females (II, 1, 3) the onset of choroido-retinal dystrophy was delayed until middle life and the size and shape of the eyeball was then so stabilized that myopia did not occur.

In other abiotrophic diseases of the retina and choroid, myopia is common but not invariable as in the affected males of the present series; for instance, Sorsby, Franceschetti, Joseph, and Davey (1952) described ten men in a family with choroideremia who were affected, of whom four were myopic, two emmetropic, two hypermetropic, and two undetermined. Myopia is fairly commonly found in retinitis pigmentosa, but many advanced cases of the disease are observed in patients who are emmetropic or hypermetropic.

It is significant that, in the present series, the onset of the disease is very early and central vision is lost very early. It might, therefore, be supposed that this early loss of central vision interferes with the mechanism by which the growth of the eyeball is so co-ordinated that the majority of people approximate to emmetropia.

Relationship to Recognized Affections

(1) Retinitis Pigmentosa

The disease in this family shows considerable resemblance, especially in the symptom of night blindness and in the ophthalmoscopic appearances, to certain types of retinitis pigmentosa, but differs from the classical picture in that it has been impossible to demonstrate the existence of an annular scotoma and in the fact that central vision in this disease is affected at a very early age, whereas in many cases of retinitis pigmentosa good central vision may be retained until middle age. On closer inspection the fundus picture also shows considerable variation from that seen in typical retinitis pigmentosa. The pigment seems to spread into the periphery, and is aggregated into irregular masses, only a few of which show something resembling the typical bone corpuscle formation of retinitis pigmentosa, and there are also white spots. In the female cases the fundus changes are even more unusual, with large masses of pigment in the periphery and intermediate zones and fine pigment deposits at the maculae. The retinal vessels are not narrowed to the same degree as in retinitis pigmentosa.

The mode of inheritance of retinitis pigmentosa varies; a dominant form occurs in about 20 per cent. and an autosomal recessive form in 37 per cent. In these cases consanguinity occurs in 25 per cent. and it has been calculated that the gene frequency in the general population is one in 71 (François, 1961). There are many sporadic cases of retinitis pigmentosa (39 per cent.), and it is probable that many of these are in fact autosomal recessive cases occurring as the result of chance mating between parents carrying the relevant gene. Only 4·5 per cent. of cases of retinitis pigmentosa are inherited according to a sex-linked pattern, although even in the autosomal cases males are affected more often than females. Falls and Cotterman (1948) have described a family with sex-linked retinitis pigmentosa in which the carrier women had normal visual acuity and fields but all showed marked tapetal reflex, and two showed abnormal colour vision. In another family the males showed typical retinitis pigmentosa and all the carrier females were normal. We have found no reports of sex-linked retinitis pigmentosa in which female carriers have shown progressive fundus lesions.

(2) Choroideremia

Many cases of this disease have been reported in the literature as atypical retinitis pigmentosa but Goedbloed (1942) and Waardenburg (1942) independently suggested this was a condition due to an intermediate sex-linked affection. McCulloch and McCulloch (1948) studied a family of over 600 members, including 33 affected and 53 carriers, and another family of eighteen with five affected and five carriers. Sorsby and others (1952), in a survey of the literature with an analysis of the clinical and genetic aspects, found the condition to be transmitted by carrier women who invariably showed peripheral pigmentary mottling of the fundus, but had no overt symptoms; it appeared that these changes in the carrier females were not progressive. In the male the earliest symptom is night blindness and the earliest fundus change is a fine granular pigmentary mottling. The condition is relentlessly progressive and exposure of the choroidal vessels is seen at an early stage; these vessels become sclerotic and gradually disappear, leaving a white reflex. It is characteristic of choroideremia that the central choroidal circulation remains intact for many years so that good visual acuity may be retained with tubular vision.

Pöllot (1912) described a family with atypical chorio-retinitis pigmentosa; the grandfather died, nearly blind, at the age of 46 and he had a brother with defective vision. The ophthalmoscopic appearances were not described. The grandfather had two daughters with good sight but they showed pigmentary changes in the fundi. Each daughter had several children with normal sight and had one son with defective vision. This family was reviewed by Waardenburg (1962), who concluded that the two male cousins in Generation III suffered from choroideremia; it is interesting that the two mothers retained good vision all their lives, one dying at 70 and the other at 80.

(3) Retinal Aplasia

For many years it has been recognized that certain infants are found to have defective sight from birth or from a very early age. At this age ophthalmoscopic examination is often negative although there may be a suggestion of optic atrophy.

Blindness, however, becomes confirmed as the children grow older and ophthalmoscopic changes become apparent. A large series of such cases was recorded by Alström and Olson (1957) and two families were described by Sorsby and Williams (1960). In these families blindness occurred in infants of both sexes and, although both dominant and recessive forms of inheritance occur, no pedigree with a sex-linked form of inheritance has been described. Moreover, in many of these families there is mental deficiency.

(4) Macular Dystrophies

In addition to the infantile and juvenile forms of cerebral macular degeneration, Stargardt (1909) described hereditary forms of macular dystrophy occurring in childhood inherited as autosomal recessive characters. Sorsby and Davey (1955) have shown that a dominant form of macular dystrophy may occur with a less sudden onset and a slow decline of visual acuity in adult life or early middle age. It is possible that there is a sex-linked form of macular dystrophy. In all these diseases, however, the anomaly is confined to the macula; there is no contraction of the visual fields and no evidence of any pathological process in the periphery of the fundus.

Choroidal sclerosis accompanies many fundus diseases but it may occur as a primary process and is probably inherited as a dominant character. It leads not to night blindness but to loss of central vision.

(5) Generalized Fundus Dystrophy

This disease, described by Sorsby and Mason (1949), affects patients at about the age of 40; there is no symptom of night blindness, the first symptom being blurred vision in one eye followed by the same complaint in the other eye. The objective signs are oedema, haemorrhages, and exudates in the central area progressing to scar formation and pigment proliferation. There is choroidal exposure and some sclerosis.

Genetic Aspects

It is clear that the disease under investigation has a predilection for the male sex; it may occur in the female sex though in a modified form. It was, therefore, considered whether the disease was inherited as an irregular autosomal dominant with sex modification. If this were so it is unlikely that the three men in the second generation would all have been quite unaffected as well as their children.

It was then considered whether the condition was a recessive sex-linked disorder. This explains the transmission of the disease by normal female carriers to their sons, but does not explain the occurrence of fundus anomaly with impairment of vision in nearly 50 per cent. of the proven female carriers.

Intermediate sex-linkage was then considered, such as occurs in some cases of retinitis pigmentosa and also in choroideremia. In these conditions, however, all the female carriers show recognizable fundus anomaly, and this anomaly is believed to be present from an early age and to be non-progressive. In the family under consideration we find that fundus lesions are present in not quite 50 per cent. of the proven carriers and the others showed no fundus anomaly at all. Moreover, in twelve young females of the third generation, no fundus anomaly whatever was

found, whereas, theoretically, 50 per cent. of the females in this generation should also have been carriers.

In spite of this there is overwhelming evidence that the condition under examination is transmitted by the X-chromosome. If it be assumed that the man (I, 1) from whom all the affected members are descended was himself affected by the condition described in his grandsons, then the following criteria for X-chromosomal inheritance are satisfied:

(1) The fully developed form of the condition appears only in men.
(2) The sons of affected men are normal and the children of these sons are normal.
(3) All daughters of an affected man are carriers.
(4) 50 per cent. of the sons of the carrier females are affected by the disease in its normal form.

In an attempt to identify the carriers in Generation III, two sex-linked characters were studied—colour blindness and the Xg blood group which Mann, Cahan, Gelb, Fisher, Hamper, Tippett, Sanger, and Race (1962) have shown to be transmitted by the X-chromosome (Race and Sanger, 1962). Unfortunately, the studies failed to solve the problem of identifying the carrier females.

Related Families.—Numerous relatives were traced and examined, but the only cases of eye disease were those found in the children of II, 3, a maternal aunt of M I, 1. The H family tree (Fig. 5), in which M I, 1 takes his place as H III, 7, shows this relationship. His cousins suffered from dislocated lenses with raised tension. This is a condition which is believed to be inherited as an autosomal recessive and this finding is, therefore, purely coincidental.

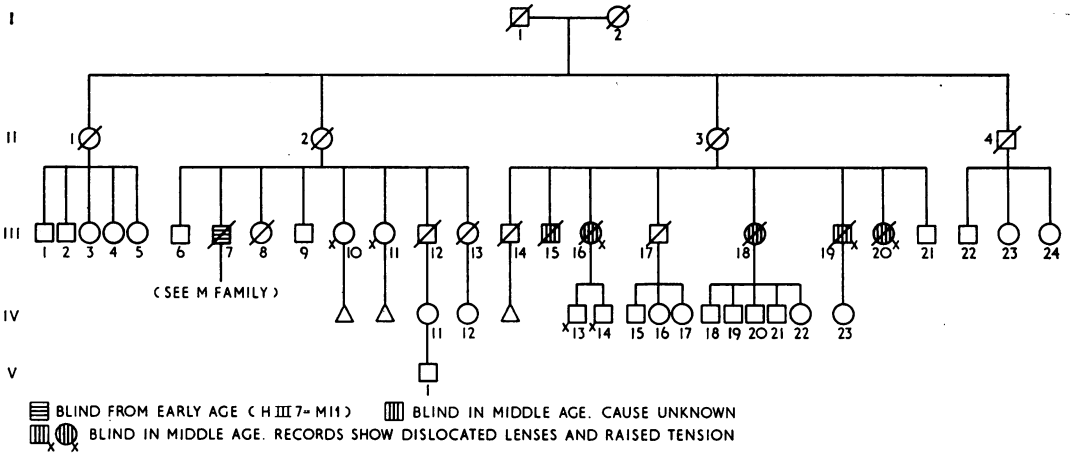

FIG. 5.—Pedigree of Family H.

Conclusion

This family may therefore be concluded to be suffering from a choroido-retinal dystrophy transmitted by the X-chromosome which in affected males leads to blindness at an early age. In carrier females delayed manifestations may occur having a polymorphic character and running a variable course which may lead to blindness in middle age.

It may be predicted that the unaffected males in Generation III will have normal children provided they marry normal spouses, not related to them. Affected males who marry normal spouses will have normal sons, but all their daughters will be carriers, and may be themselves affected.

It must be expected that 50 per cent. of the apparently normal females of Generation III are carriers, but it has not yet been possible to identify them. If these carriers should marry normal spouses, half their sons will be affected and half their daughters will be carriers. If a carrier female should marry an affected cousin, all the daughters of this union would be carriers, and some (the affected homozygotes) would possibly be severely affected.

The clinical picture presented by the affected males in the family under discussion does not fit in with any of the affections defined above. The onset of the disease is very early and its course rapidly progressive, but the onset is not so early as to lead to the suspicion of blindness at birth or in early infancy. The clinical condition may, therefore, be regarded as intermediate between that seen in retinal aplasia, which is of earlier onset, and that seen in intermediate sex-linked retinitis pigmentosa, which is of later onset.

The clinical condition of the proven carrier females is of particular interest. The two youngest (II, 8, 9) sisters are apparently normal, though each has one affected son. Of the five elder sisters three (II, 1, 3, 6; M family, Fig. 1.), show fundus changes of an "atypical retinitis pigmentosa" type with visual impairment. Further studies after an interval of 10 years or so may indicate a higher incidence of fundus changes in the seven sisters of Generation II.

Summary

An hereditary disease of the choroid and retina is described which differs in certain respects from other known diseases. There is evidence that it is transmitted by the X-chromosome. In the male, the condition is detected in childhood. Some of the carrier women show abnormalities of the fundus accompanied by visual impairment; these manifestations occur in middle age and are probably progressive.

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APPENDIX

M FAMILY

AFFECTED MALES

I 1 (died in 1950 aged 70) is known to have been blind from an early age and was certified blind by an ophthalmic surgeon in 1920, but the surgeon has since died and the records are no longer available.

III 1 (born 5.2.31) was thought to have normal sight until the age of 12 when he was found to have defective vision and sent to a Blind School. He subsequently obtained employment in a Blind Workshop. Visual acuity is perception of hand movements, with moderate nystagmus and slight posterior cortical lens opacities. The optic discs are pale, with very narrow retinal vessels, and considerable pigmentation over all the fundus, in irregular masses, and in some places of the bone corpuscle type (Fig. 6). He is myopic about −8 D sph.

III 2 (born 4.6.33)
III 7 (born 1941)
III 10 (born 8.10.42)
III 14 (born 3.11.37)
III 20 (born 28.5.46)
III 21 (born 26.11.54)
III 22 (born 23.9.56)

All these men and boys have defective vision with fundus changes varying according to their age.

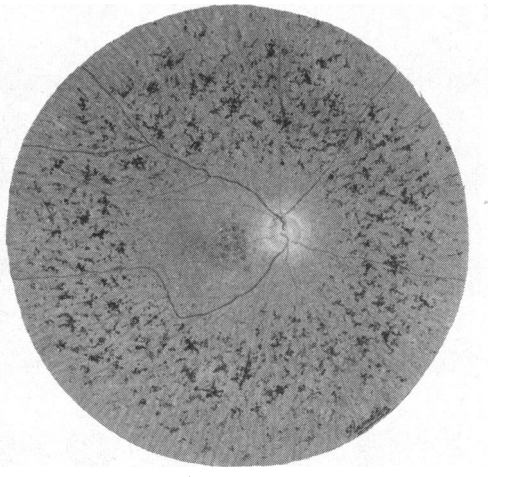

FIG. 6.—Fundus appearance of III. 1.
Figs. 6—8 represent males of M family.

III 26 (born 11.5.52), the propositus, had been referred at the age of 9 to a school clinic for assessment of suitability for education as a blind or partially sighted child. His mother said that his sight had been defective since he was 3 years old. He held things very close to his eyes to examine them and appeared to have particular difficulty in seeing in a dim light.

He had normal skin colour, medium brown hair, and blue irides. On May 25, 1963, when the boy was 11 years old, the uncorrected visual acuity was 1/60 in each eye. With correction −10 D sph., −2 D cyl., axis 20° for the right eye and −10 D sph., −2 D cyl., axis 160° for the left eye, he could read 6/60 with each eye. He could not distinguish any Ishihara colour plates. There was no nystagmus.

Perimetric examinations of the visual fields showed generalized contraction in all quadrants except the inferior temporal. In the upper nasal quadrants the fields were contracted to 15°. It was not possible to plot the central visual fields, but no annular or arcuate scotoma was present.

The optic media were clear permitting a good view of the fundi (Fig. 7). The choroidal vessels show up clearly and the first impression is that of an albinotic fundus; at the posterior pole and especially around the optic disc, the choroidal vessels are sclerotic and the background appearance is abnormally pale. The optic disc shows a generalized grey waxy pallor. The retinal arteries are narrower than normal and there is arteriolar sclerosis. Abnormal pigmentation is present in the intermediate and peripheral zone of the retina throughout its circumference. It takes the form of irregular masses, sometimes assuming a bone corpuscle shape.

Physically and mentally the boy is normal apart from the eye condition.

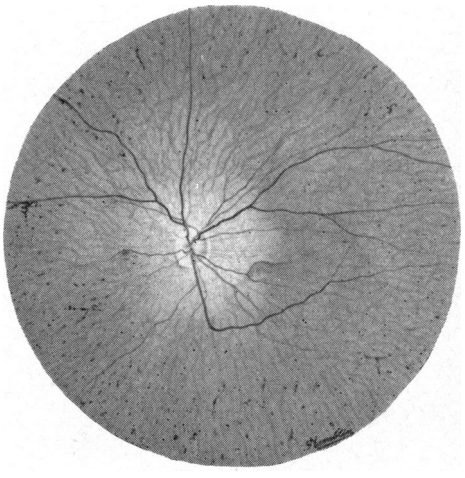

FIG. 7.—Fundus appearance of III. 26.

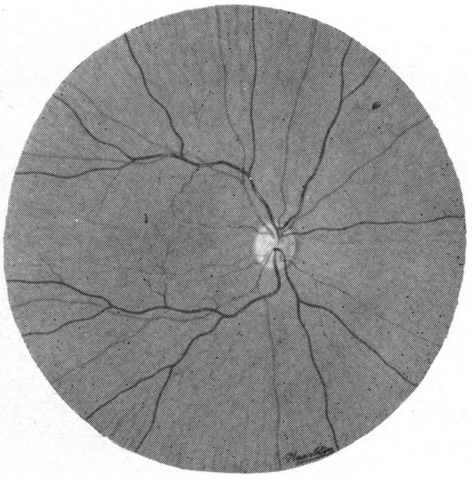

FIG. 8.—Fundus appearance of III. 30.

III 30 (born 27.3.60), is too young to test visual acuity, but his mother suspects that his vision is not as good as that of his brother and sister. He is myopic about −6 D sph. The left fundus shows a mottled appearance in the upper nasal quadrant otherwise the fundus appearance is normal. The right fundus shows a spot of abnormal pigmentation in the upper nasal quadrant (Fig. 8). This is the youngest known affected male; he shows only slight fundus changes which would probably have been missed had the family history not been known.

AFFECTED FEMALES

II 1 was unaware that she had any eye defect, but both fundi show isolated patches of abnormal pigmentation in the periphery. The discs appear normal, the arteries rather narrow, and the veins normal. The macula shows some abnormal pigmentation. Visual acuity 6/9 right, 6/18 left. Visual fields almost normal (Fig. 2).

II 3 was aware that her sight was defective and sought advice in a Hospital Eye Department in 1962, where a diagnosis of atypical retinitis pigmentosa was made. Visual acuity in the right eye, 6/18 improved to 6/9 with +0·5 D sph., and 6/12 emmetropic in the left. The right vitreous shows asteroid hyalitis. The right fundus shows a somewhat atrophic disc. There is diffuse mottling throughout the fundus with patches of bone corpuscle-like pigmentation and also solid lumps of pigment elsewhere, the appearance being suggestive of an inflammatory retinitis. The left fundus is less abnormal but the upper nasal quadrant shows a few isolated patches of bone corpuscle pigmentation. Both maculae show mottled pigmentation (Fig. 3).

II 6 noticed her sight failing from the age of 20, but did not seek advice until she was in her 40's when she was found to be certifiably blind. The vision in the right eye is hand movements and in the left 1/60 with correction −10 D sph. The right visual field is contracted almost to fixation point; the left shows contraction in the upper nasal quadrant. The discs are slightly pale; there is marked choroidal pattern and sclerosis and widespread abnormal pigmentation, some of it of a bone-corpuscle formation (Fig. 4).

UNAFFECTED FEMALES

I 2, wife of I 1, is dead but is reputed to have been normal.

The wives of the men in Generation II are normal. There are four women in Generation II (II 4, 5, 8, 9) who have had affected sons but themselves show no clinical evidence of choroido-retinal disease. They have 6/6 visual acuity in each eye and normal colour vision, and are emmetropic. None shows a significant tapetal reflex.

In Generation III there are twelve girls or young women, all of whom have 6/6 visual acuity and normal colour vision, and are emmetropic. Their fundus appearances are normal. None shows a tapetal reflex sufficiently marked to be significant. In the following cases a tapetal reflex was detectable though the appearance was felt to be within the range of normality: III 4, 13, 15, 17, and 28, and V 1 (a daughter of III 4), a moderate tapetal reflex of a similar type was also observed.

UNAFFECTED MALES

II 2, now deceased, is said to have had good sight and to have had several children with good sight.

II 7 has 6/6 visual acuity in each eye, normal fundus appearances, and normal colour vision; his six children have been examined and appear to be normal.

II 10 is unmarried; he has 6/6 visual acuity in each eye, normal fundus appearances, and normal colour vision.

In Generation III there are nine young men or boys who are normal, and all approximately emmetropic; those old enough to be tested have 6/6 visual acuity and normal colour vision.