CHOROIDEREMIA: A CLINICAL AND PATHOLOGIC REVIEW

BY *Clement McCulloch*, M.D.*

THOMAS L., who lived in the south of Ireland shortly before 1850, took fatter pigs to market and regularly obtained a better price than did any of his neighbors. After a while it was discovered that some time before the pigs were to be sold he blinded them; they no longer ran about the barnyard and, therefore, were fat when slaughtered. The old women of the neighborhood said there would be a curse on Thomas which would blind him and visit his children for seven generations.

Thomas was Protestant and in the part of Ireland where he lived there were no Protestant boys for his seven girls to marry. Therefore, in 1850, he emigrated to Canada with his two sons and his seven daughters. By that time he was going blind and the old women knew that the curse had started to act.

Thomas was successful in his endeavors, as all his children did marry. His two sons had large families. I have examined over 90 descendants of the two boys and have found no sign of blindness amongst them. Of the seven daughters one had no children. However, all of the other six had large families, up to fifteen children, who have been traced in some detail. The descendants of Thomas L. form a lineage of about 1600 individuals, of whom I have seen more than 600.

The disease these descendants have is a chorioretinal degeneration, commonly given the name choroideremia. Since the affected males have the full form of the disease they can be considered as cases. They go blind over the course of their lifetime. The females show the incomplete form of the disease, have no significant visual defect, and can be recognized only by the appearance of the fundus. They can be considered as carriers.

*From the Department of Ophthalmology, University of Toronto.

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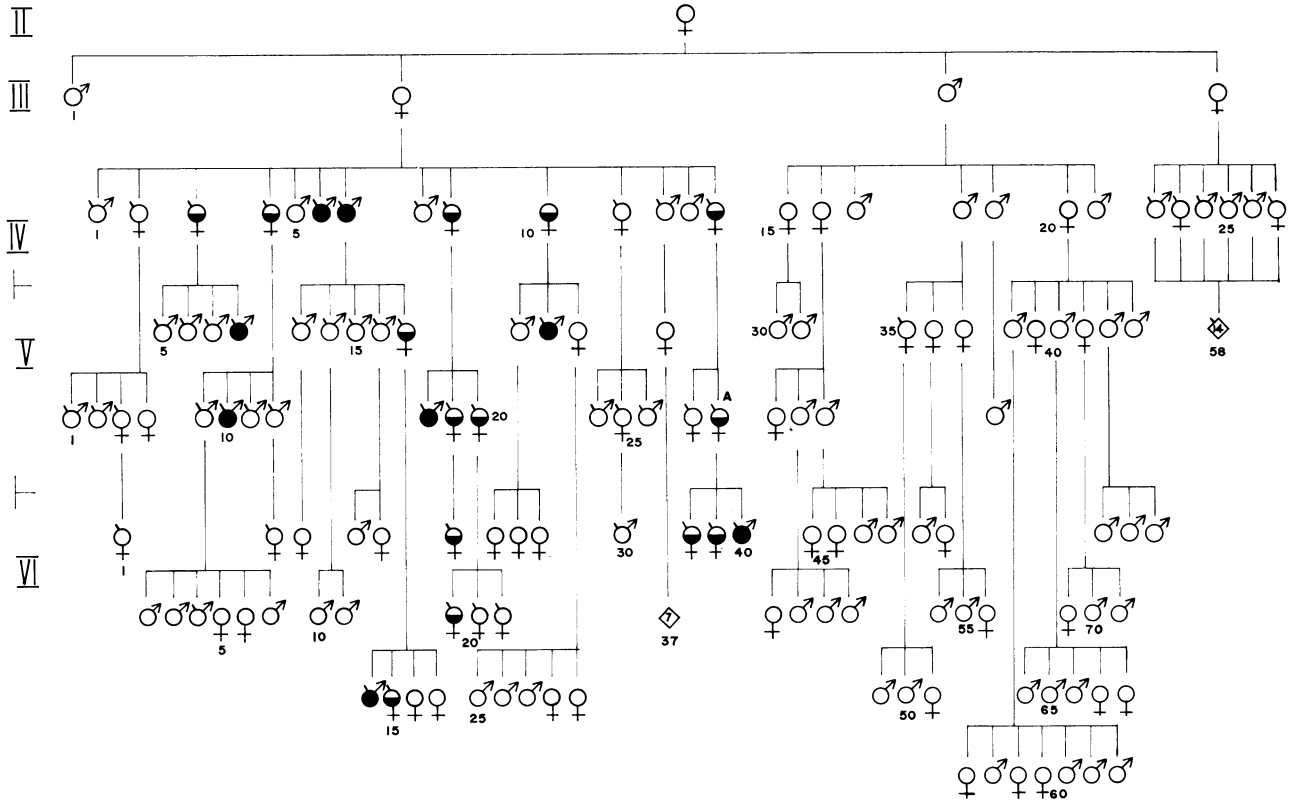

FIGURE 1

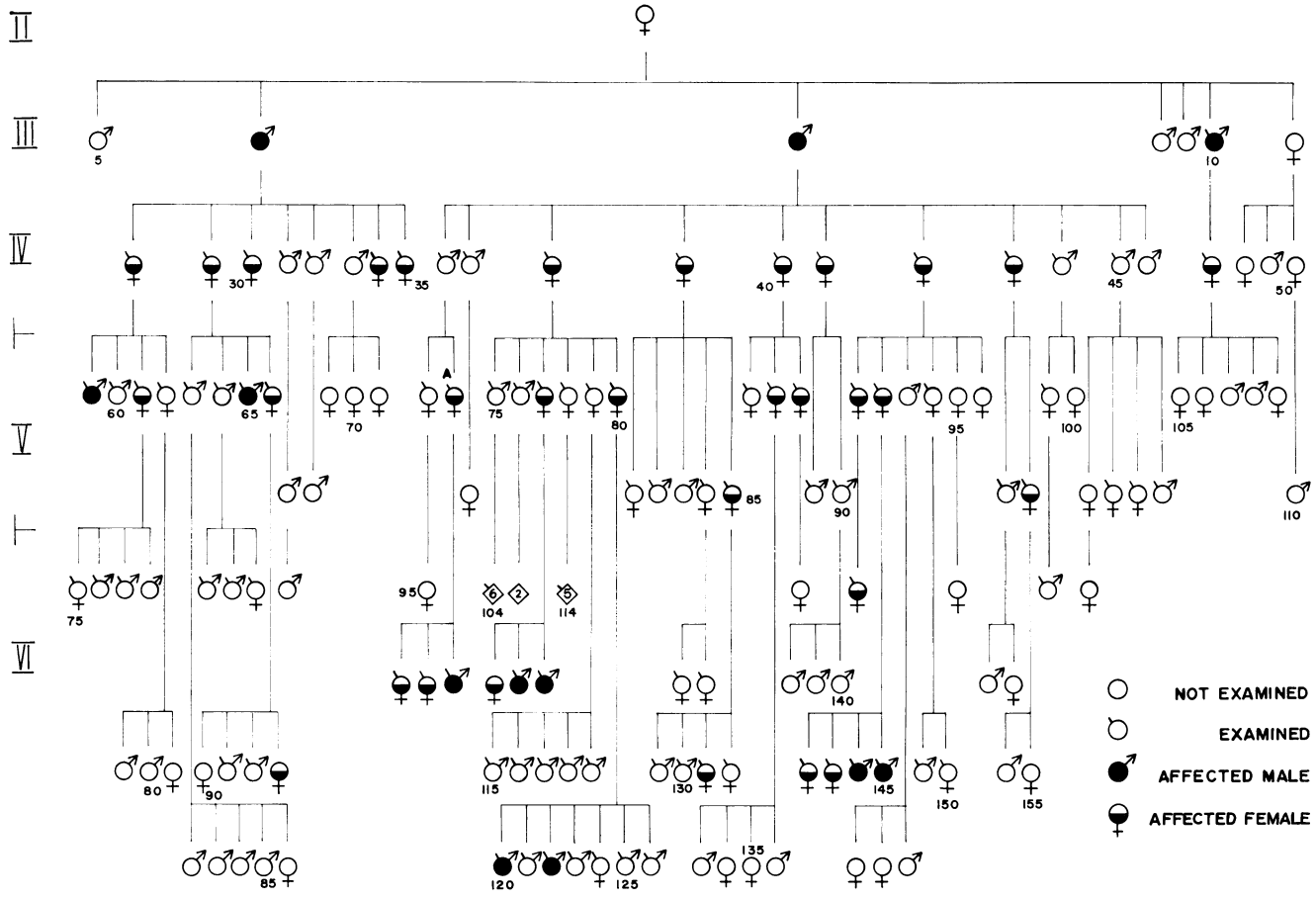
II
III
IV
V
VI
NOT EXAMINED
EXAMINED
AFFECTED MALE
AFFECTED FEMALE

FIGURE 2

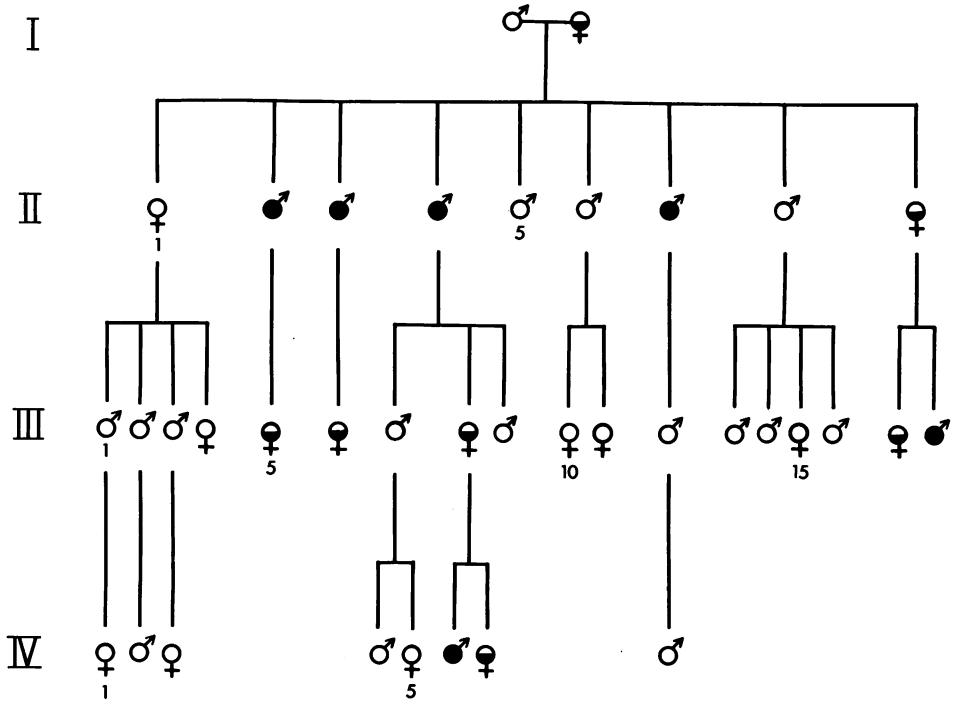

FIGURE 3

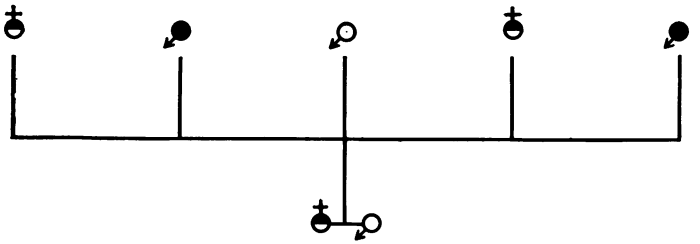

FIGURE 4

I have seen two other families with this disease, both families being much smaller, but both confirming the findings in Thomas L.'s family. Because the L. family is so large I will use only one branch of it, plus the other two families, to review the condition.

The family trees of the one branch of the larger family (RL) and of the smaller families (S and K) are shown in Figures 1 through 4. There is one cousin marriage, the offspring of which are noted as A in the figures. Otherwise, throughout the families the hereditary pattern is consistent; the passage being from males to all their daughters and from females to some of their sons and some of their daughters. The actual transmissions are shown in Tables 1 through 3, by generation for the large family and for the whole of each of the smaller families.

These tables show that an affected male transmits the disease to none of his sons and all of his daughters. Therefore, the penetrance as far as men are concerned is 100 per cent for their female offspring, 0 per cent for their male offspring, and approximately 50 per cent for all their children.

The tables also show that the affected female transmits the disease to some of her sons and some of her daughters. On considering the figures in the tables one gets the impression that penetrance is less than 50 per cent amongst sons and more than 50 per cent amongst daughters. However, I do not think that that causal conclusion is valid, as the collection of data is far from unbiased. It was noticeable, particularly among the older generations, that affected males were not discovered. Repeated cross checking with different members of the family was only partially successful in finding these men. There is a strong family feeling that these men have the "curse" and that they should be hidden away and forgotten. The fact that among males the distribution of affected individuals in generation 6 is about 50 per cent is probably a reflection of the investigator's initiative and of the

TABLE 1. FAMILY RL–PERSONS AT RISK

Generation		Female to male	Female to female	Male to male	Male to female
2	Affected			0	7
History	Unaffected			2	0
3	Affected	3	1		
History	Unaffected	5	2		
4	Affected	2	5	0	12
Examined	Unaffected	4	2	6	0
5	Affected	6	12	0	1
Examined	Unaffected	17	9	4	0
6	Affected	9	12	0	1
Examined	Unaffected	10	8	0	0

TABLE 2. FAMILY S–PERSONS AT RISK

	Female to male	Female to female	Male to male	Male to female
Affected	6	3	0	3
Unaffected	3	1	3	0

TABLE 3. FAMILY K–PERSONS AT RISK

	Female to male	Female to female
Affected	2	2
Unaffected	1	0

fact that the young mothers wish to know and plan for the future of their boys. The figures of penetrance for girls are not affected by this bias. The female has no visual symptoms and the family does not know the diagnosis until she is examined.

There must be considerable weighting of the data because of the unavoidable problems of collection. Despite this, there is sufficient evidence to indicate that penetrance in the families is continuing unabated.

CLINICAL APPEARANCE

It is 23 years since my father and I studied this family.[1] At that time we saw males showing all stages of the disease and postulated a regular progression of changes from youth to old age. I have now re-examined many of these men and can see that advancement of the disease does occur as we predicted.

The young male, shortly after birth, shows a severely and widely pigmented fundus (Figures 5 and 6). The pigment epithelium is grossly disrupted, great masses of pigment lying behind and in the retina. Particularly in the midperiphery the picture can be chaotic.

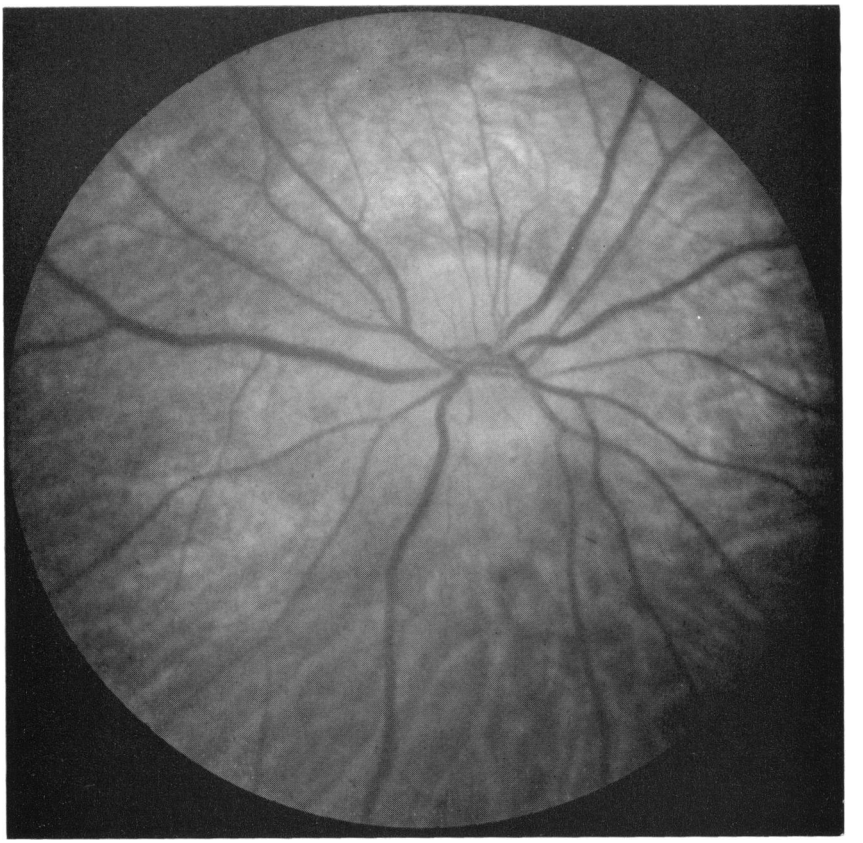

FIGURE 5
Young male.

Any pattern that is present cannot be related to the retinal vessels but in the grossest terms may follow the choroidal vasculature. The pigment characteristically is in grains and chunks. Between the pigment and lying deep to it are pale yellow areas, with an orangy-yellow glow, which I take to be regions of atrophy of pigment epithelium and thinning of choroid. If these areas are smaller they have a more yellow color, if larger they tend to become whitish, revealing bared sclera. Toward the periphery this disruption decreases and some of the reddish color of the normal fundus is visible. Similarly, toward the disk and macula the normal pattern and color of the fundus becomes dominant. In the macular region the usual reddish reflex is present and the choroidal structure would seem intact. In some cases

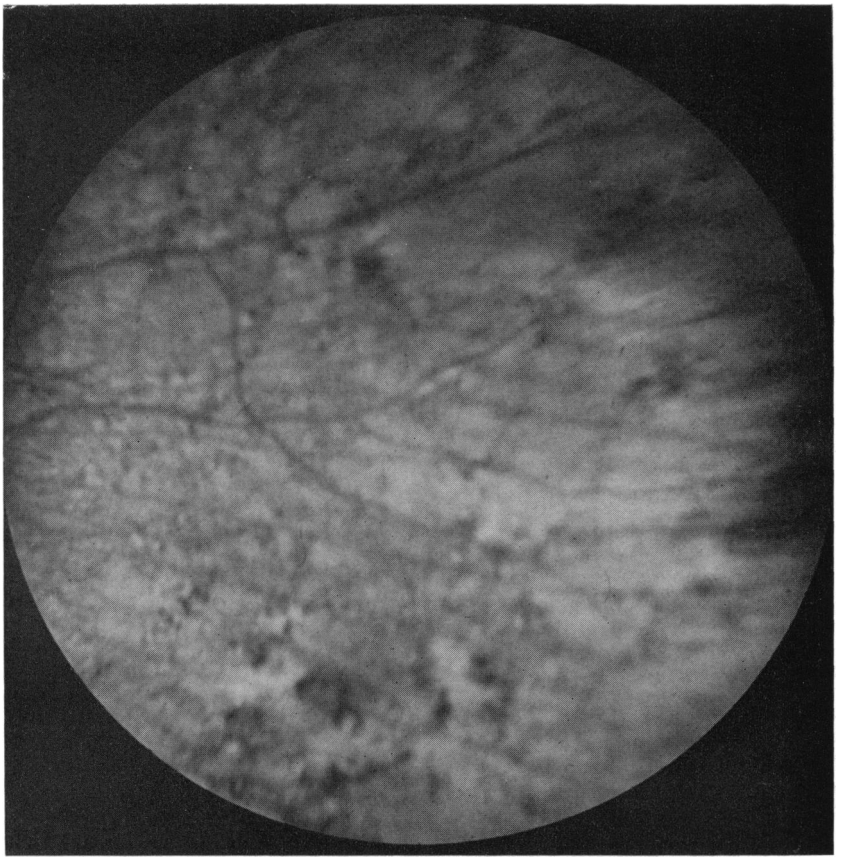

FIGURE 6
Young male. Changes in the midperiphery.

a cluster of small particles of broken pigment lie in the retina at the macula; these would seem to have come from peripheral areas of shattered pigment epithelium. About the disk there may be a granular pigmentary change but this is not as severe as in the midperiphery. A common finding is a pale halo of choroidal thinning about the disk. The retinal arteries and veins are normal in size and are not sheathed; the disk itself is of normal color. The vitreous is not degenerate; the lens is clear. The remaining structures of the eyes are normal.

As the patient ages, the pale areas in the midperiphery extend and coalesce, the smaller orange-colored areas increasing and becoming white, the whitish areas of exposed sclera becoming larger (Figure

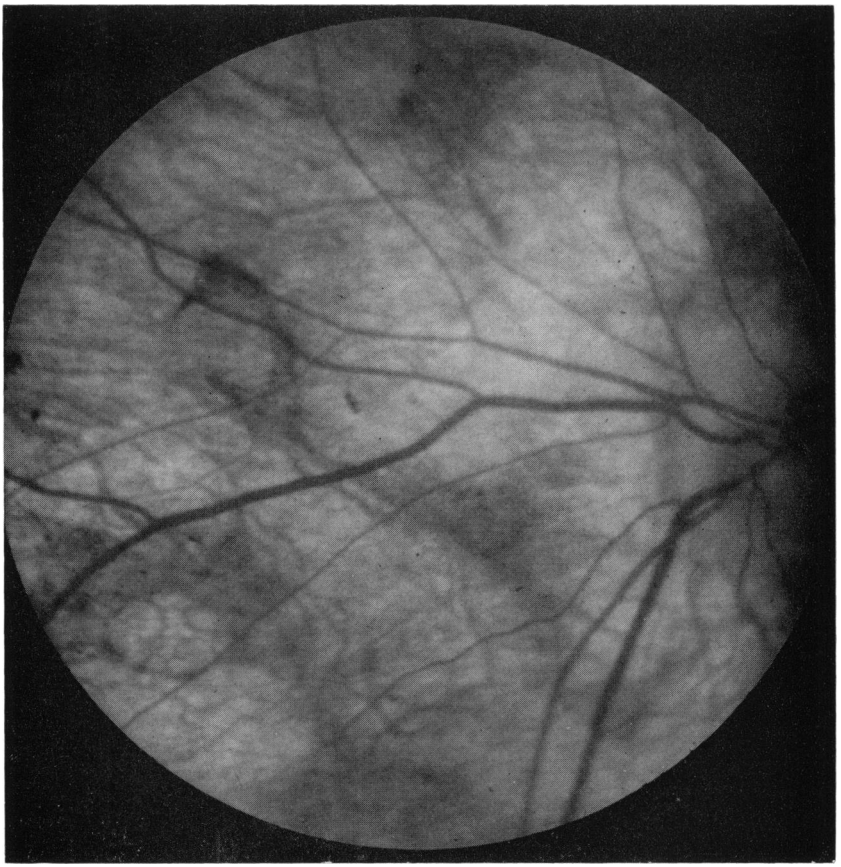

FIGURE 7
Moderate changes in a male.

7). The massive chunks of pigment in the midperiphery gradually disappear. By his mid-twenties the male shows large equatorial areas of whitish atrophy. In the far periphery, areas of red reflex remain with some pigmentary disarray still present in the region. The macula still appears spared and has the reddish color of the normal fundus. Large exposed choroidal vessels protrude at the edges of this region but shrink rapidly in all directions except toward the disk. In that direction the vessels seem to cross a paler, atrophic area to make connection with large loops of choroidal vessels that lie about the disk. At the disk the normal red fundal reflex remains and here also large loops of choroidal vessels border the region. The retinal vessels

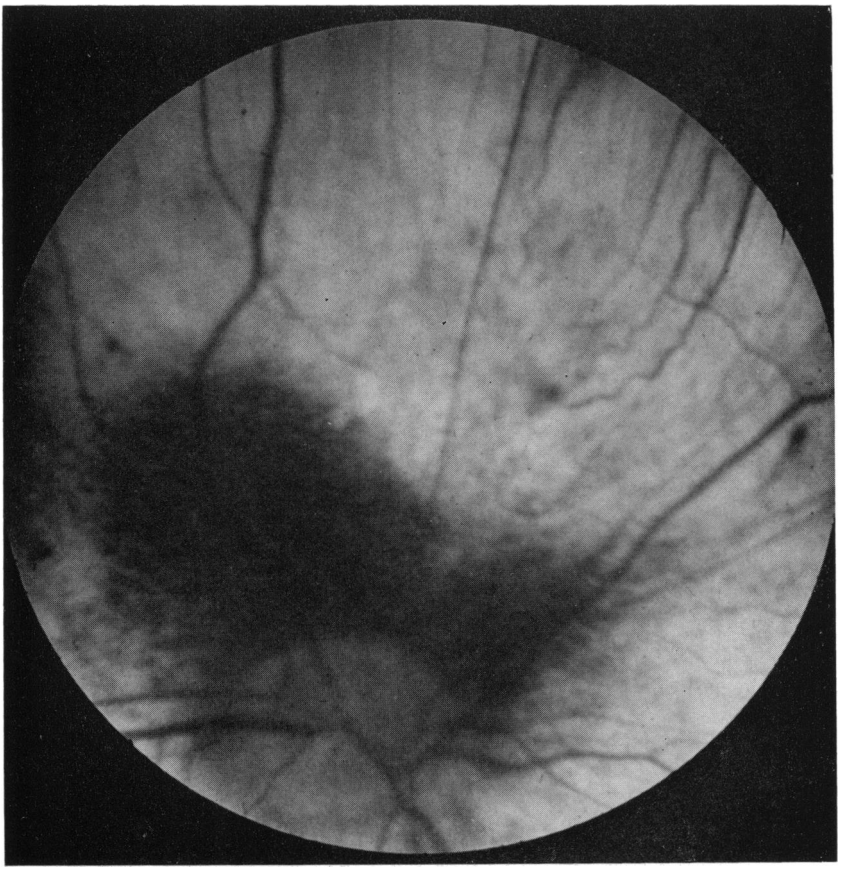

FIGURE 8
Moderate changes in a male.

themselves appear normal and the disk does not show any waxy atrophy as one might see in retinitis pigmentosa. There may be some fibrillary change in the vitreous but this is really not significant. The lens remains clear.

At an older age, such as a man of forty-five, the whole of the mid-periphery of the fundus is brilliantly white (Figure 8). Apparently, the pigment epithelium and choroid are completely missing and we are looking directly upon sclera. In the far periphery a few reddish areas of normal fundus color may still be seen. There are isolated, scattered clumps of pigment on the extensive white background but these are only remnants of what was there previously. Some of this

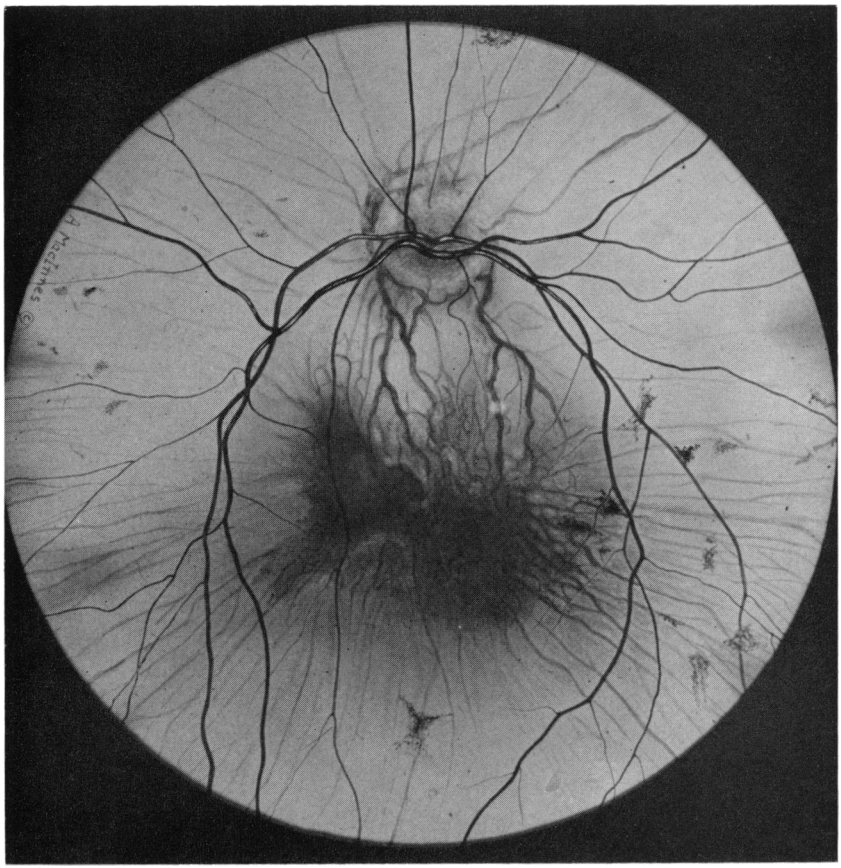

FIGURE 9
Advanced case in a male.

pigment may lie neighboring the retinal vessels and there is indication of a distribution according to the retinal vasculature. At the macula is an area of reddish reflex, which is approximately the size of the disk; along its border lie loops of choroidal vessels. Some of these extend toward the disk where there may be a small area of reddish color, usually on the side of the disk toward the macula. Around the disk the atrophy is extensive, so that white of sclera reaches to the margin of the nerve. It is hard to judge whether the nerve is atrophic or not. It gives the impression of normal color but against the white fundus that is difficult to decide on. There is no sheathing of the retinal vessels and no narrowing as in retinitis pigmentosa. There may

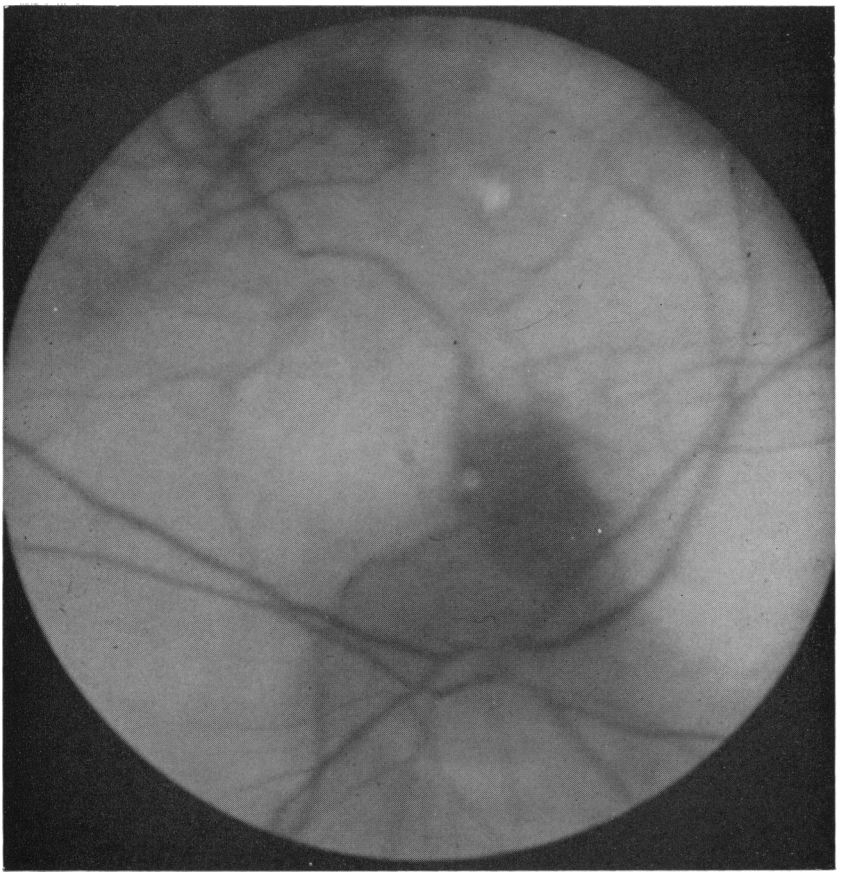

FIGURE 10
Advanced case in a male.

be degeneration of the vitreous but this also is not marked as in retinitis pigmentosa; the lens tends to remain clear.

In old age the changes continue (Figures 9 and 10). In the far periphery it is no longer possible to find a red reflex. The area of reddish color at the macula becomes very limited. The atrophy about the disk continues until only a small patch of redness bordered by loops of choroidal vessels remains at the macula. The fundus then appears white with the retinal vessels continuing to trace their course across a glistening background. The retinal vessels still are of normal caliber. The vitreous may be degenerate, but this does not seem out of keeping with the patient's age. The lens may be cataractous, but

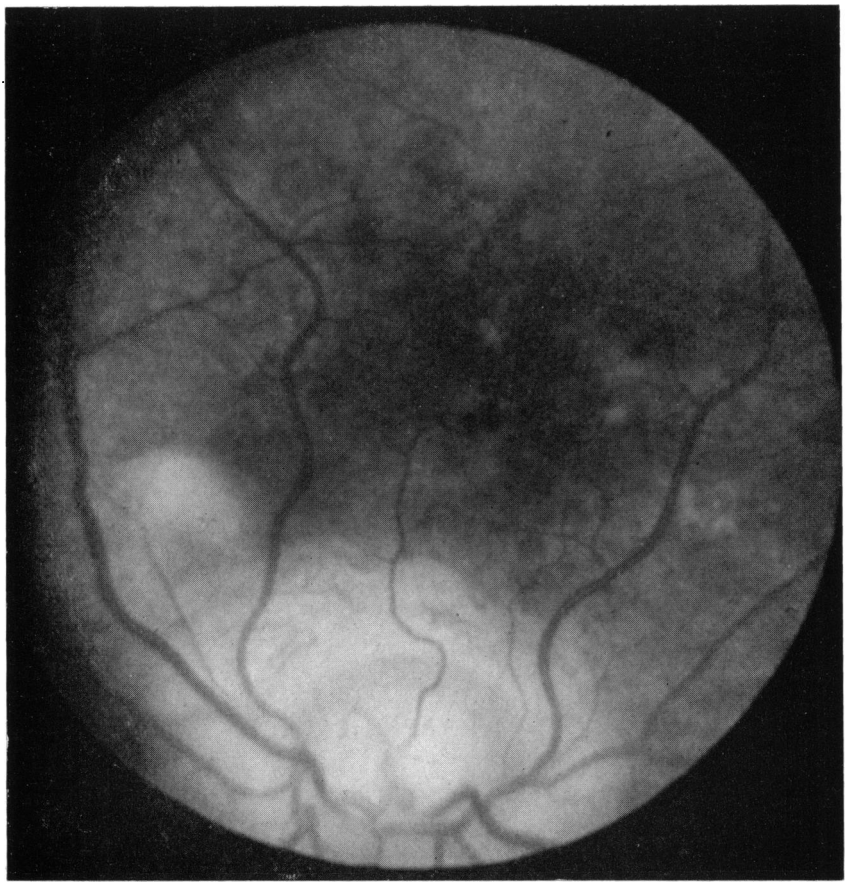

FIGURE 11
Female carrier.

the incidence of this change is low and probably not larger than would be normal for the age group.

This appearance of the fundus in the males does show some variation from individual to individual. In a youth of seven to ten years of age there may be a variation from severe pigmentary change to moderate atrophy. In their twenties, whereas some individuals may show a minimum of atrophy, most are starting to develop extensive atrophy. By 45 years of age there are some men who are almost blind. By this age all are showing some atrophy, at least in a moderate amount. By 60 years of age practically all are blind. There may be

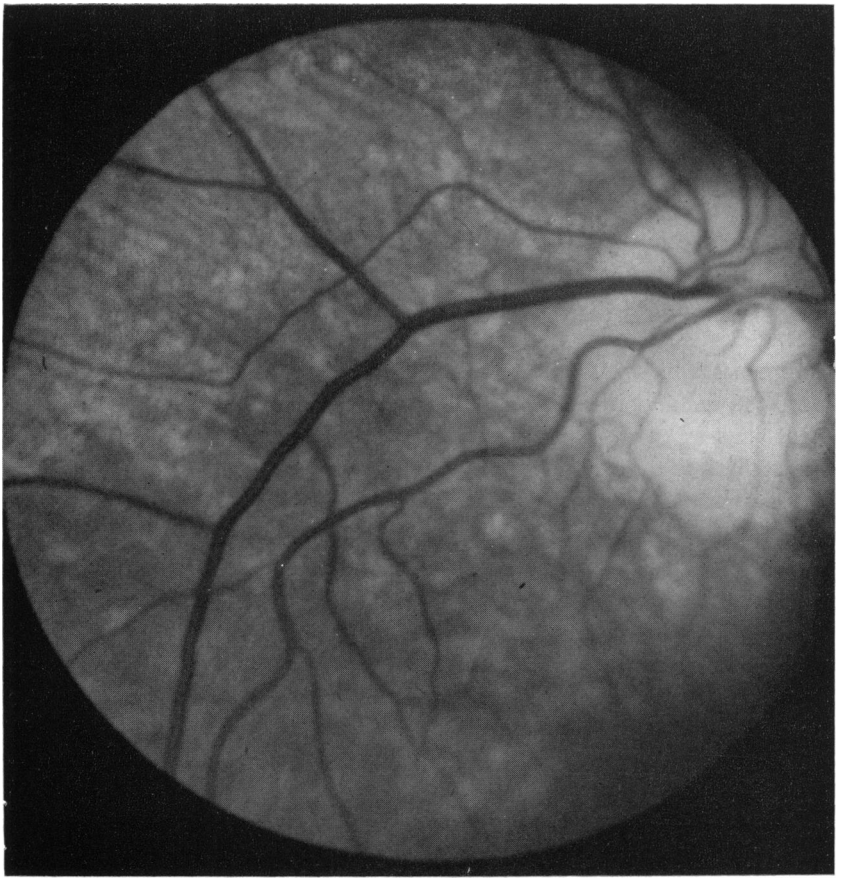

FIGURE 12
Female carrier.

some individuals with a very small field remaining but the majority have no light perception or just the trace of light perception upon careful searching. The fundus is severely affected at that stage in all males.

The appearance in the fundus of the female bears some resemblance to the very early changes found in the male (Figures 11 and 12). There is some stippling of pigment in the midperiphery. The pigment consists of small, squarish chunks. This can involve one or all quadrants of the fundus. Among the pigment, which seems to lie in the substance of the retina, or behind the retina, there are patches of

yellowish translucence, where apparently pigment epithelium is defective and one is seeing through into the choroid and sclera. In the macular region the fundus appears essentially normal. Occasionally, when the pigmentary change in the midperiphery is marked, pigment granules are aggregated in the macular region to form a dark ball. The area around the disk may be pale; the disk itself is normal. There is no narrowing or sheathing of the retinal vessels. The far periphery also shows some pigmentary change but this is usually mild. In its minimal form the change in the female fundus may occupy only one or two quadrants and easily can be overlooked. However, once the characteristic chunky pigment is located, the diagnosis of a carrier state is assured, the appearance being quite typical. In its most marked form the female fundus can show great disruption of pigment with great masses of pigment lying in chunks and streaks in and behind the retina, with accompanying atrophy of pigment epithelium and yellow-white light coming through.

In the female, or carrier, there is a peculiar ring of atrophy about the disk. The region is pale, a yellowish or whitish glow from choroid and sclera is present, and choroidal vessels can be distinguished. The atrophic ring is about one-quarter of a disk diameter in width and is not progressive. The disk itself is of normal color, the retinal vessels are not narrowed. The vitreous is normal and the lens is clear. There is no abnormality in the anterior segment of the eye.

I have checked the fundi of females seen 23 years ago against the appearance at a recent examination. The abnormalities in the female are not progressive and the description of the fundi recorded 23 years ago tallies closely with the current findings. The one exception that I could establish was concerning the ball of pigment seen at the macula in some of the females. This, 23 years later, was much thinner. Apparently the broken pigment lying in the retina had gradually been transported away.

There may be an occasional female in whom there is some progression of the change in the fundus. Harris and Miller describe one case from the larger family (AL 23) in which the fundi presented the atrophic appearance of the male and the patient showed loss of field and night blindness.[2] Fraser and Friedman also describe such a case.[3] I have found two females who complain of blindness at night. One of these patients has large atrophic patches in the midperiphery and bizarre midperipheral defects in the visual field; the other has a severe pigmentary change with no scotoma demonstrable by perimetry, done in the patient's own home with makeshift arrangements.

VISUAL ACUITY

In the female, visual acuity is normal. Even with pigmentary impregnation of the macula, acuity is maintained. In the male, in youth and middle age visual acuity does not fall until the visual field is tremendously reduced. It is quite remarkable, confirmed on a number of examinations, that patients with a one- or two-degree field may have close to normal visual acuity. One often wonders how a person can possibly maintain acuity with such small fields. Of course, near the end, acuity drops rather rapidly to 20/200 and less, and eventually all sight is lost.

VISUAL FIELDS

The visual fields in the female are intact. There may be some flattening of the peripheral isopters that could be brought out by static perimetry. This has not been available to us. However, at least two females in the family do show loss of peripheral field. One was studied by Harris and Miller and has been referred to. The other has marked choroidal atrophy in the midperiphery. This patient shows patchy midperipheral loss of field to a 3/1000 white test object. These areas of loss correspond to large regions of atrophy in the fundi. It can be assumed that she has rather irregular lakes of low sensitivity in the midperiphery. The other females tested have full fields with adequate isopters to medium and small test objects.

The earliest field change in the male seems to be patchy loss of midperipheral vision. This takes the form of lowering of sensitivity. In the young male the loss of field seems to correspond to the larger patches of atrophy that are present in the fundi. The patchy and irregular loss leads to most bizarre scotomas (Figure 13). As the male gets older, the loss of visual field becomes more marked. The areas of loss of sentivity spread and deepen to an absolute scotoma in the midperipheral region, extending from about 20 to 50 degrees from fixation. This scotoma tends to break through to the periphery in an unpredictable manner (Figure 14). As the disease progresses, peripheral vision is gradually encroached upon, and, similarly, the central island of vision shrinks irregularly. At an advanced stage there is a small irregular field of about 2 to 3 degrees at the center (Figure 15) and, occasionally, a small speck of light perception in the far periphery, particularly the lateral periphery. Finally, visual acuity drops, the central island disappears, and vision falls to light perception and, then, no light perception.

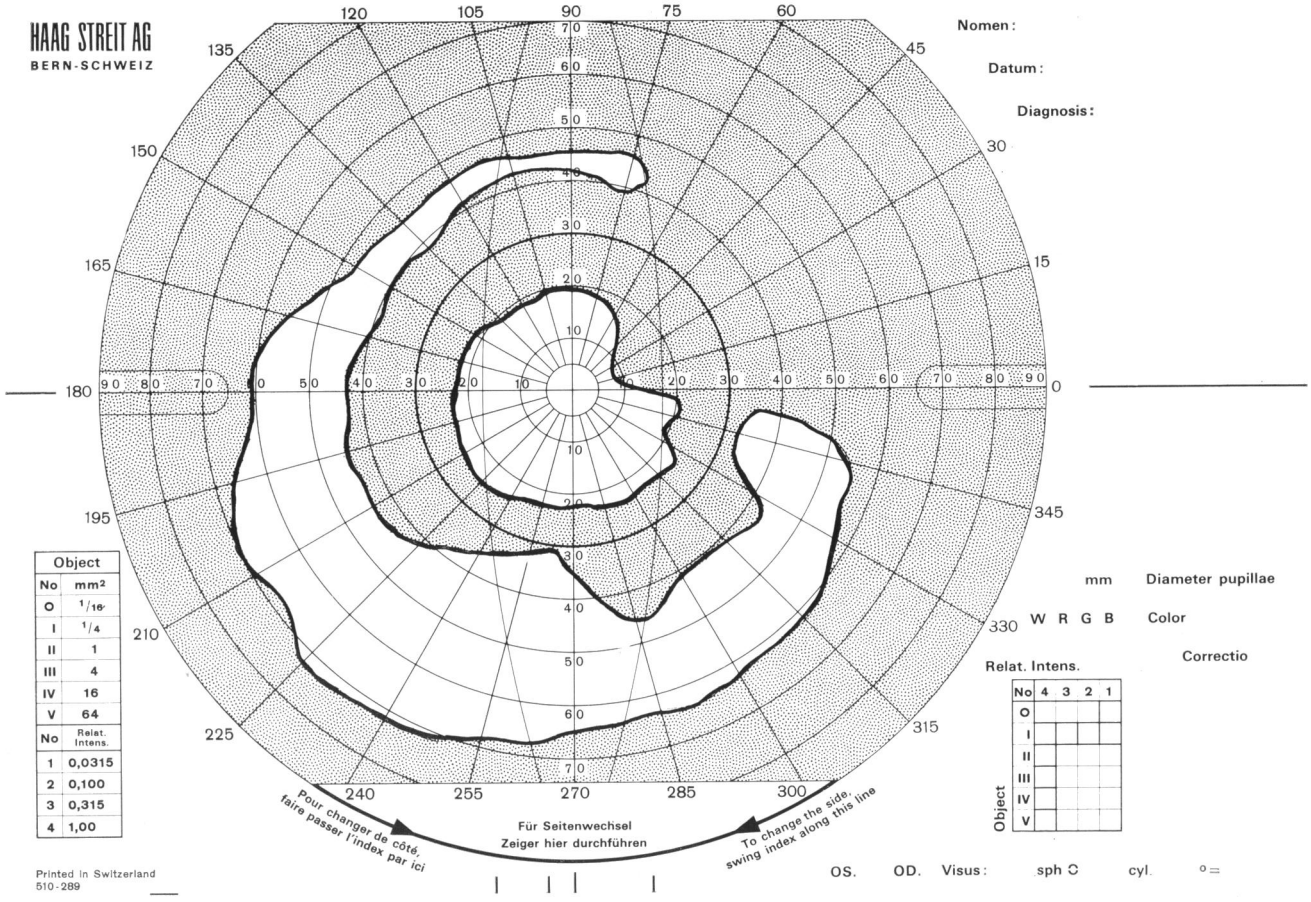

FIGURE 13
Field from a male showing moderate changes.

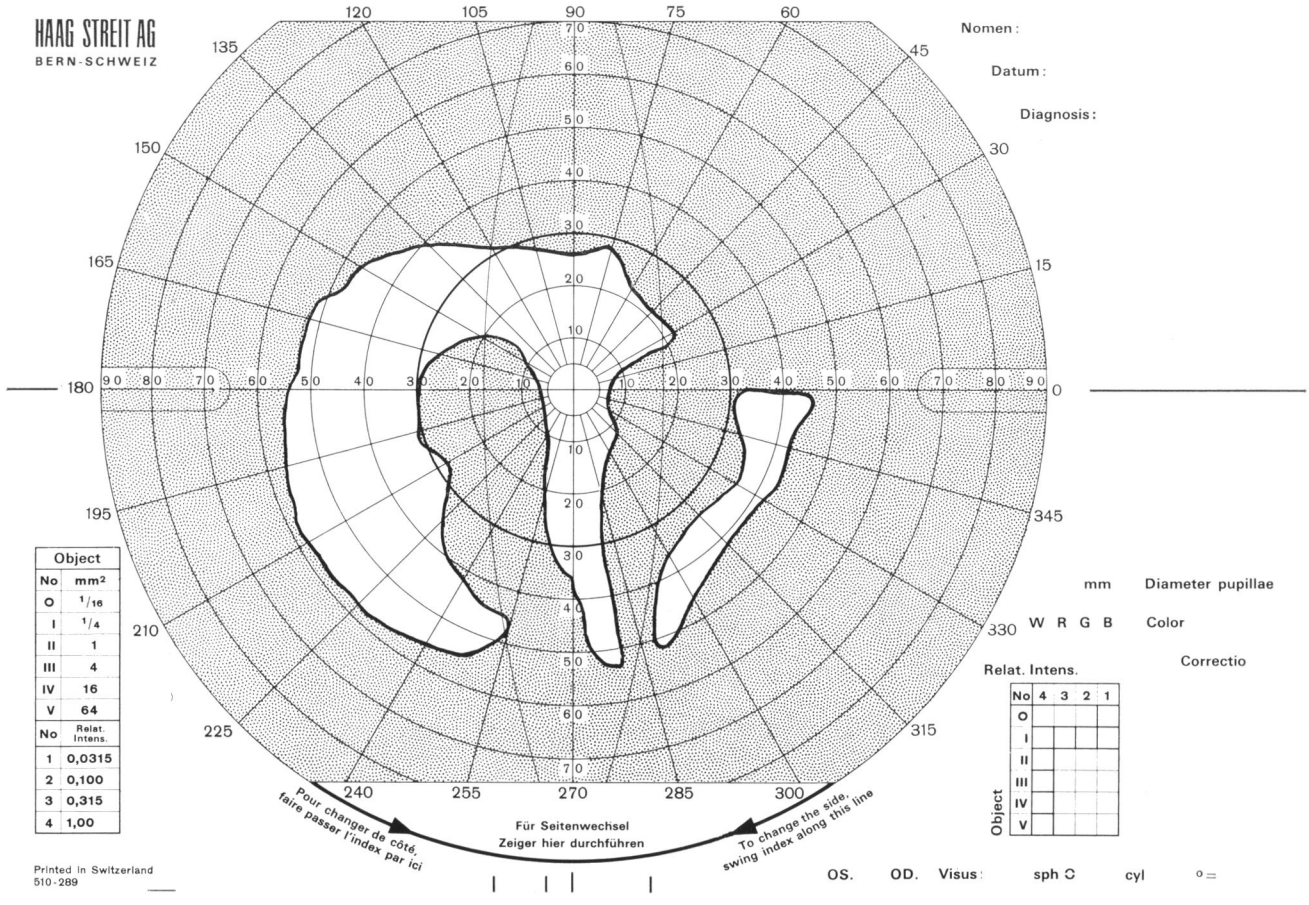

FIGURE 14

Field from a male showing moderate changes in the fundi.

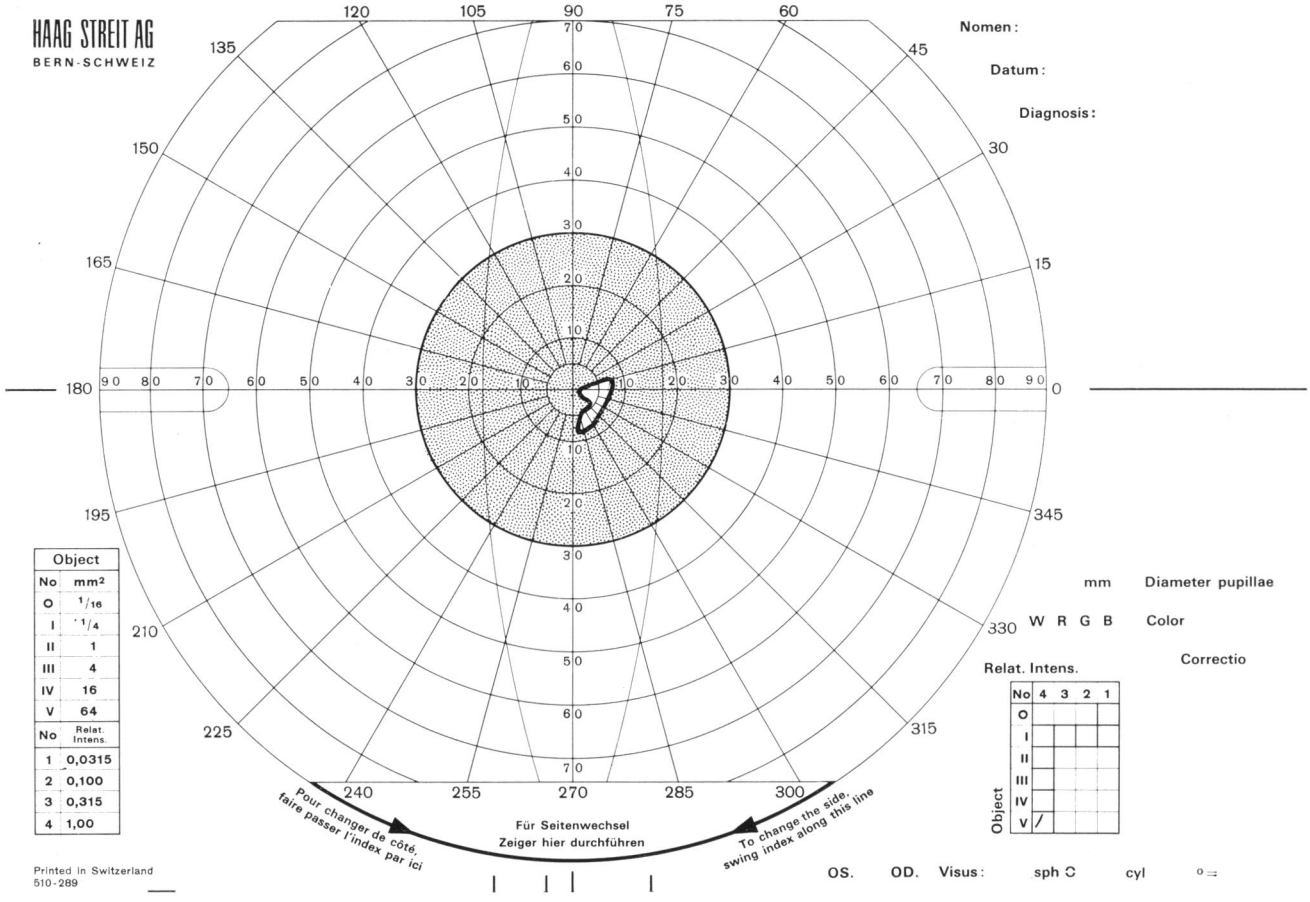

FIGURE 15
Field from a male in an advanced stage of the disease.

COLOR VISION

Tests for color vision have been done on a number of members of the family. Some general statements concerning color vision can be made.

The females have normal color vision. In a few of the females who have marked changes in the fundus there is a suggestion of poor discrimination, as tested with the Farnsworth 100-hue test. Because of the over-all distribution of the errors on the Farnsworth test, there is no clear-cut indication of a defect for blue.[4] Ordinary screen tests by the Ishihara or the Hardy-Rand-Rittler plates do not indicate any defect.

The males at an early stage of the disease show poor discrimination when tested with the Farnsworth test, similar to that found in the advanced females. As the disease progresses in the male, discrimination becomes even poorer. When the disease in the male is well advanced and the field is small, the subjects are not able to do the Ishihara, the Hardy-Rand-Rittler, or the Farnsworth test. The deficient answers received when doing these tests might be assumed to be due to a marked defect of color perception, but this conclusion does not seem to be correct. These patients can still accurately name colors. What appears to be the explanation is that a man who has a two-degree field cannot see the whole number in an Ishihara plate and can see only an individual disk from the Farnsworth test. As a result it is almost impossible for him to decipher either the letters in the Ishihara plate or to assess the gradation of hue in the Farnsworth test (Figure 16). It would appear that he probably has no major defect for color but has an inability to do the tests due to reduction of the field to an extremely small, central area. If there is any specificity in the defect in the male, it is toward a deficiency in blue perception.

Cross-over linkage studies of color vision in the family, to detect the relationship of the allele for choroideremia and that for color vision, are being undertaken. However, at the moment it appears that there is no defect for color vision in this family that can be used for a linkage study. This is rather remarkable, in view of the size of the family, and makes one wonder if the two defects are mutually exclusive.

ELECTRORETINOGRAM

Electroretinography has been done on five affected males and five affected females. Three of the men were old with advanced disease; two of the men were young. All five men had extinguished electroretinograms with no response. The five women all showed normal

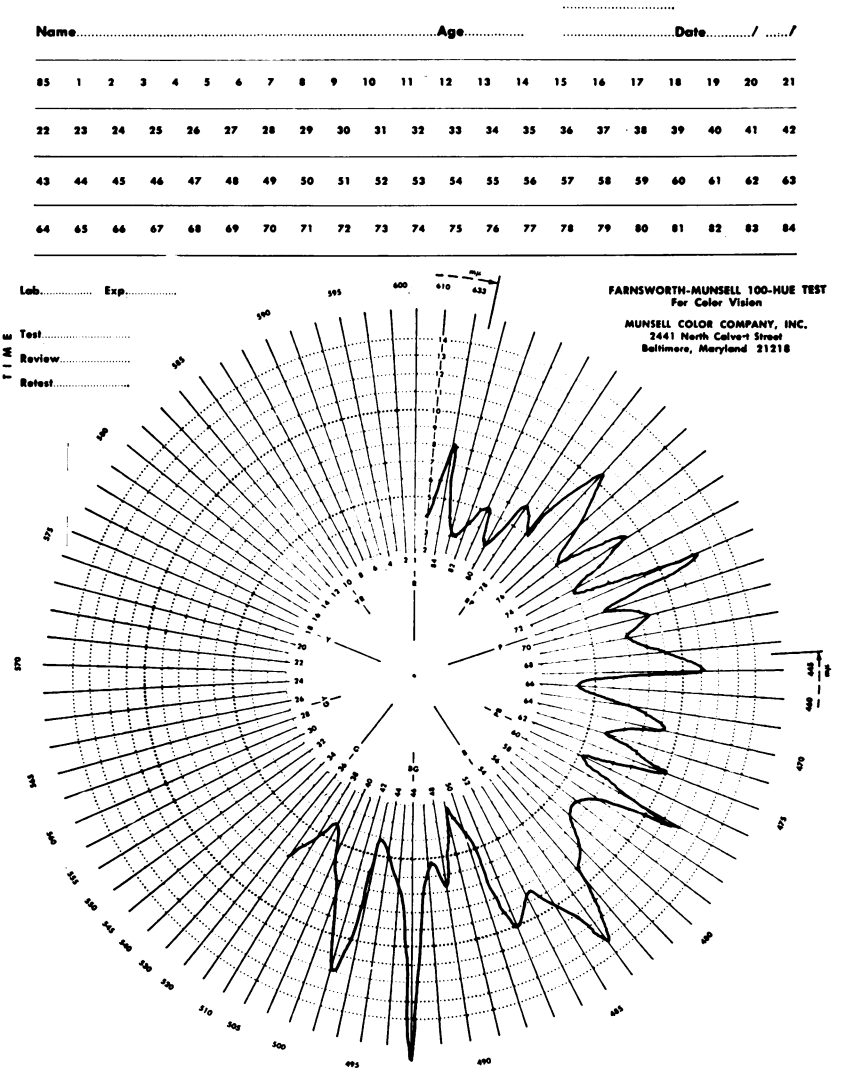

FIGURE 16
Plotting of Farnsworth 100-hue test, from a male with moderate changes.

electroretinograms, with voltages between 150 and 250 mv (Figure 17). I cannot speak with authority on the shape and size of the α and β waves. Despite the fact that the two younger men had reasonable vision no electrical response was obtained.

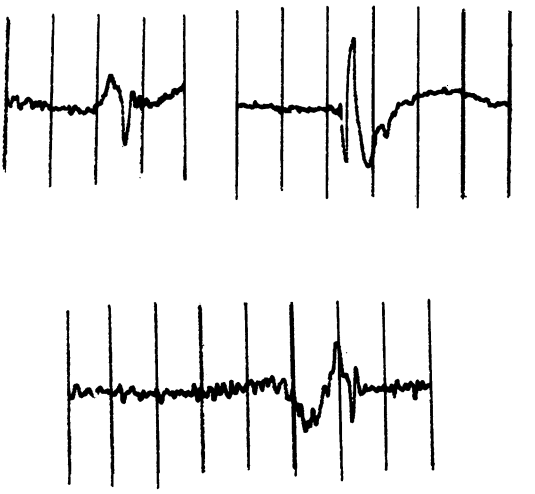

FIGURE 17
Electroretinograms from three females.

NIGHT VISION

Dark-adaptation trials were done on 5 males and 3 females using the Goldmann Haag-Streit Adaptometer. The females' night vision was found to be essentially normal, with intact scotopic and photopic phases of the adaptation curves and normal scotopic levels. The two younger men were found to have only the photopic part of the adaptation curves. After 45 minutes there was a further slight drop in the curves, suggesting very slow or late adaptation (Figure 18). The three older men could not locate the test object, even at the highest brightness levels.

KARYOTYPES

Six determinations of karyotype have been attempted on members of the family, 3 males and 3 females. In 5 of these the number of chromosomes and the appearance of the chromosomes were normal; there was no evidence of abnormality in the chromosomal pattern. In the sixth person, a male, there was peculiar and abnormal clumping of the cells on tissue culture and a chromosomal count could not be made.

FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography has been done on three males and three females. The males show little or no leakage of the contrast medium,

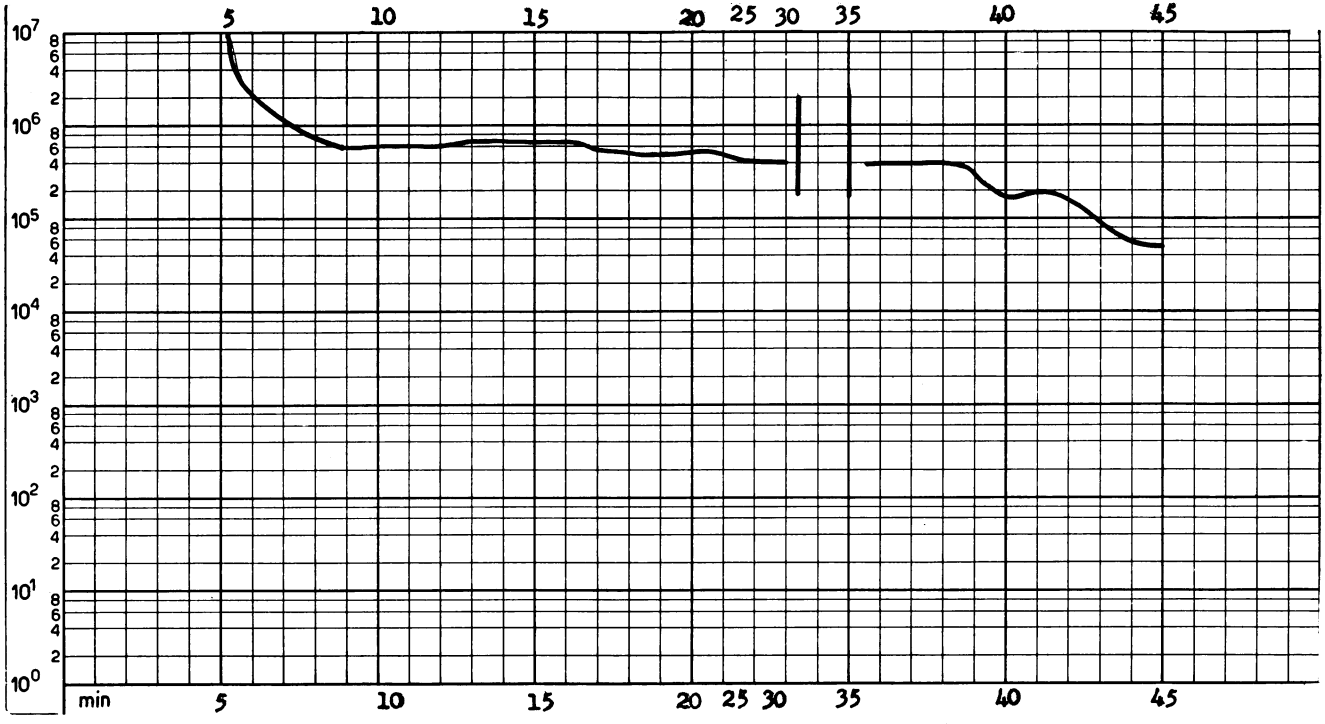

FIGURE 18
Dark-adaptation curve from a young male.

even at those locations where choroidal vessels remain – about the disk and macula (Figures 19–21). The females show leakage of contrast material at the pale yellow patches and atrophic areas (Figures 22–24). One would postulate that the choroidal vessels remaining in the males are sclerosed and that fluorescein does not easily pass out of them.

PATHOLOGY

Five eyes have become available to us. Four of the five happen to be eyes from elderly males showing well advanced disease. Two have been reported at a meeting of the American Academy of Ophthalmology and Otolaryngology.[5] One has been described in the Canadian Journal of Ophthalmology.[6] One eye has been obtained by Dr. Michael Shea from a patient who did not belong to my families but who has all the clinical appearance of choroideremia and has a family history indicative of choroideremia. It will be described. Finally, we have had one further eye, which has not been previously reported. One other eye is reported in the literature.[7]

CASE I. (COURTESY OF DR. SHEA)

The patient, E.P., a 43-year-old male, had noted gradual reduction of night and day vision for 13 years. A cataract had developed in the left eye and cataract extraction had been done in June 1966. Following this procedure a pigmented mass was noted near the equator; this was photocoagulated, and, when there was no significant change in the tumor, the eye was enucleated in September 1966. The general appearance of the fundi had been that of gross loss of pigment epithelium and disappearance of choroidal vessels. There had been a central island of red choroidal vessels and pigment epithelium, which extended to the disk. The clinical diagnosis was choroideremia.

This eye will be reported in detail by Drs. M. Shea and W. S. Hunter. I will discuss only the retina and choroid. My interest centers on the fact that the changes were in keeping with the findings in the other eyes with choroideremia but were the least advanced that have been seen so far.

The internal limiting layer of retina was intact. The nerve-fiber layer was atrophic. Two layers of cells, the inner and outer nuclear layers, could be traced across the retina. The rods and cones and pigment epithelium were missing except at the posterior pole. The choroid was withered, having only sparse fibrous bundles and a few vessels.

At the macula, Bruch's membrane and choroid were intact and there was a layer of shrunken pigment epithelial cells lying on Bruch's membrane (Figures 24 and 25). The cones were present, lying as individual projections with spaces between them. A fibrillar tissue, apparently the remnant of Henle's fiber layer, lay internal to the cones. The cones that were present

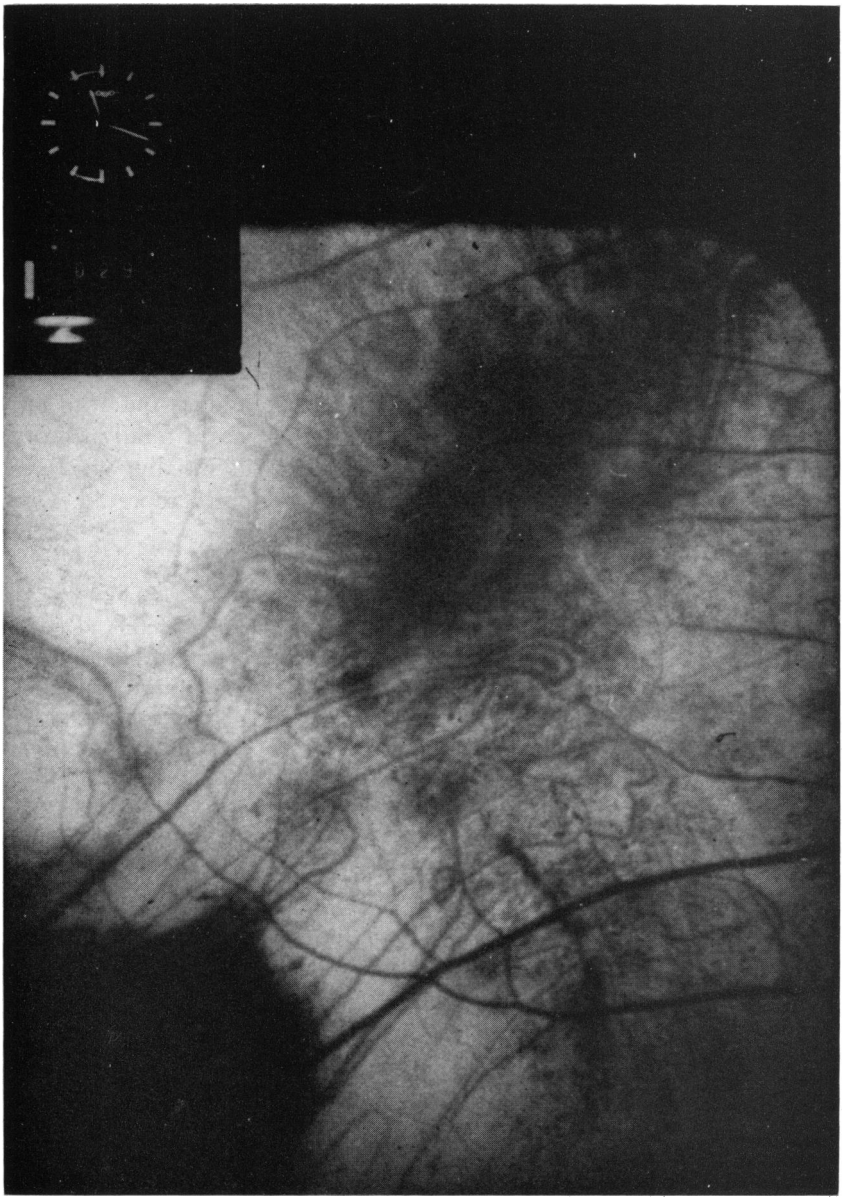

FIGURE 19
Fluoescein injection, arterial phase. Male with advanced disease.

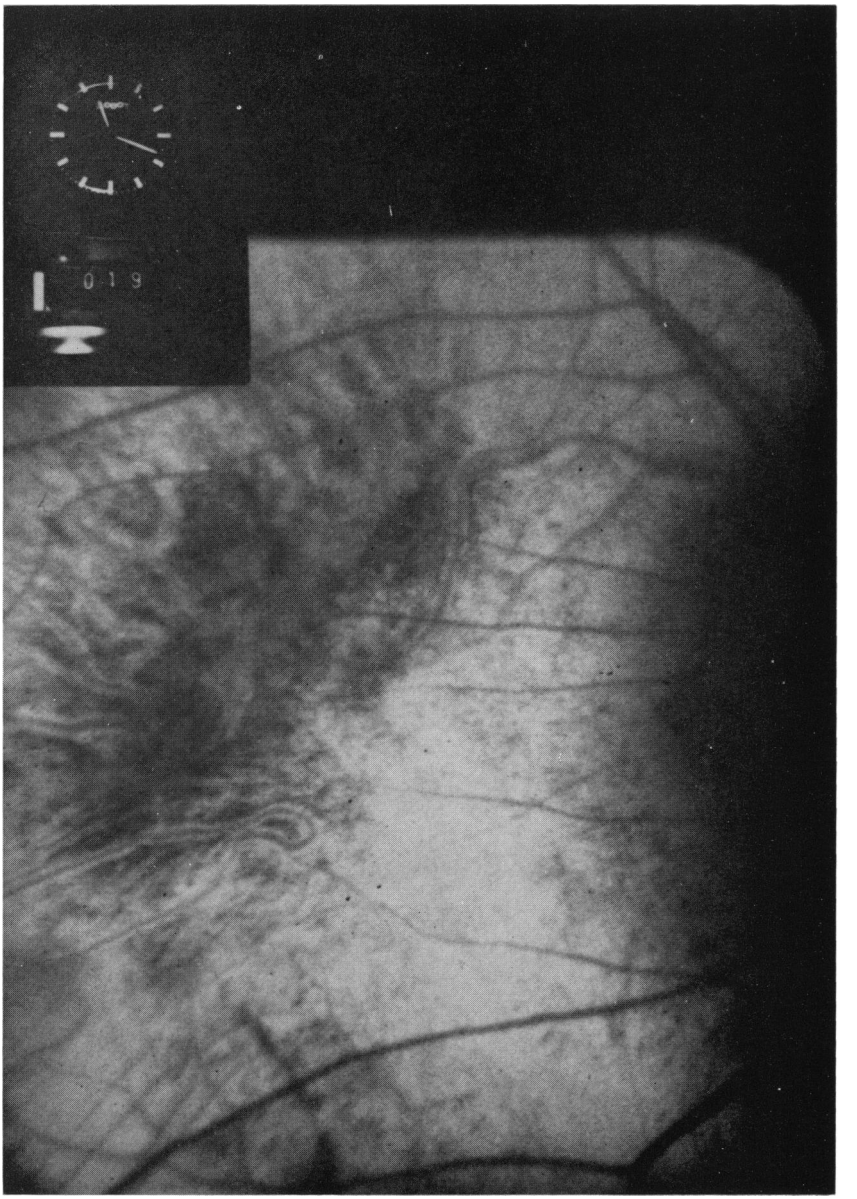

FIGURE 20
Fluorescein injection, venous phase. Same patient as shown in Figure 19.

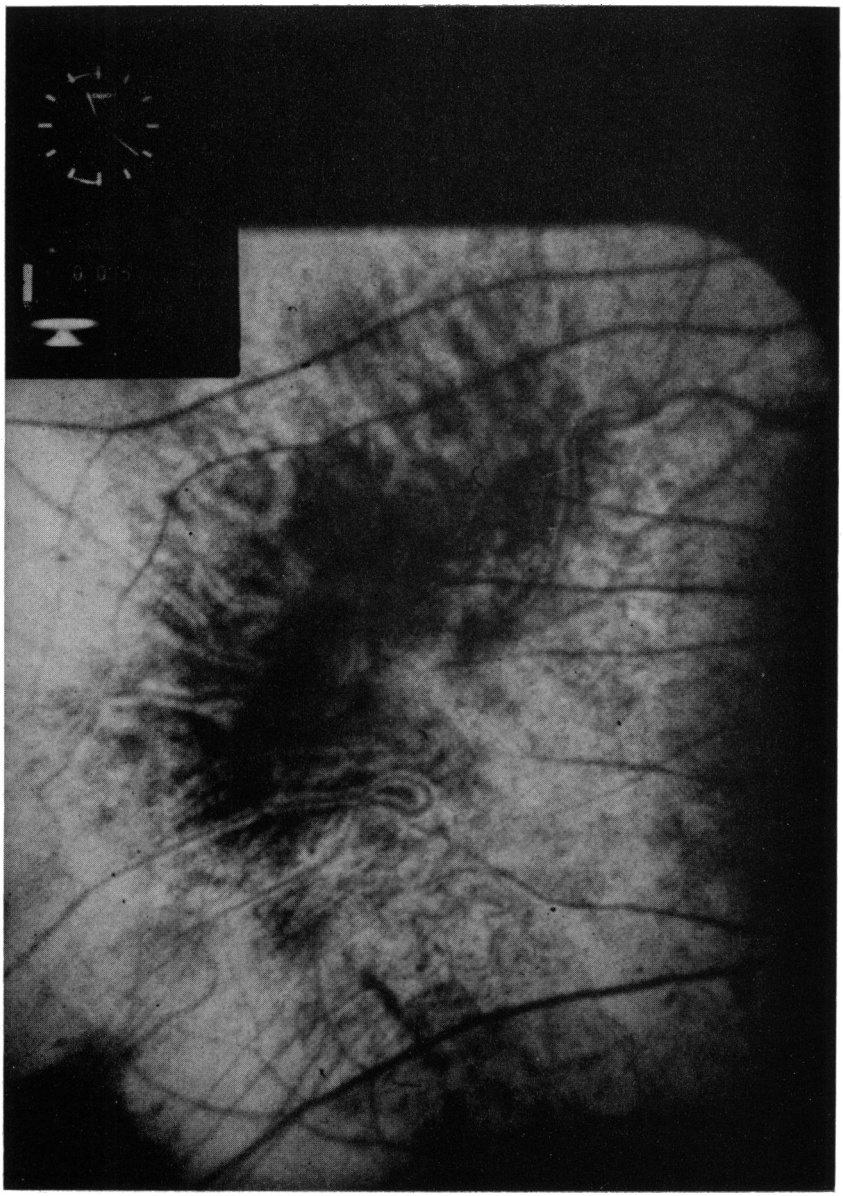

FIGURE 21
Same patient as shown in Figure 19, about 90 seconds after injection of fluorescein.

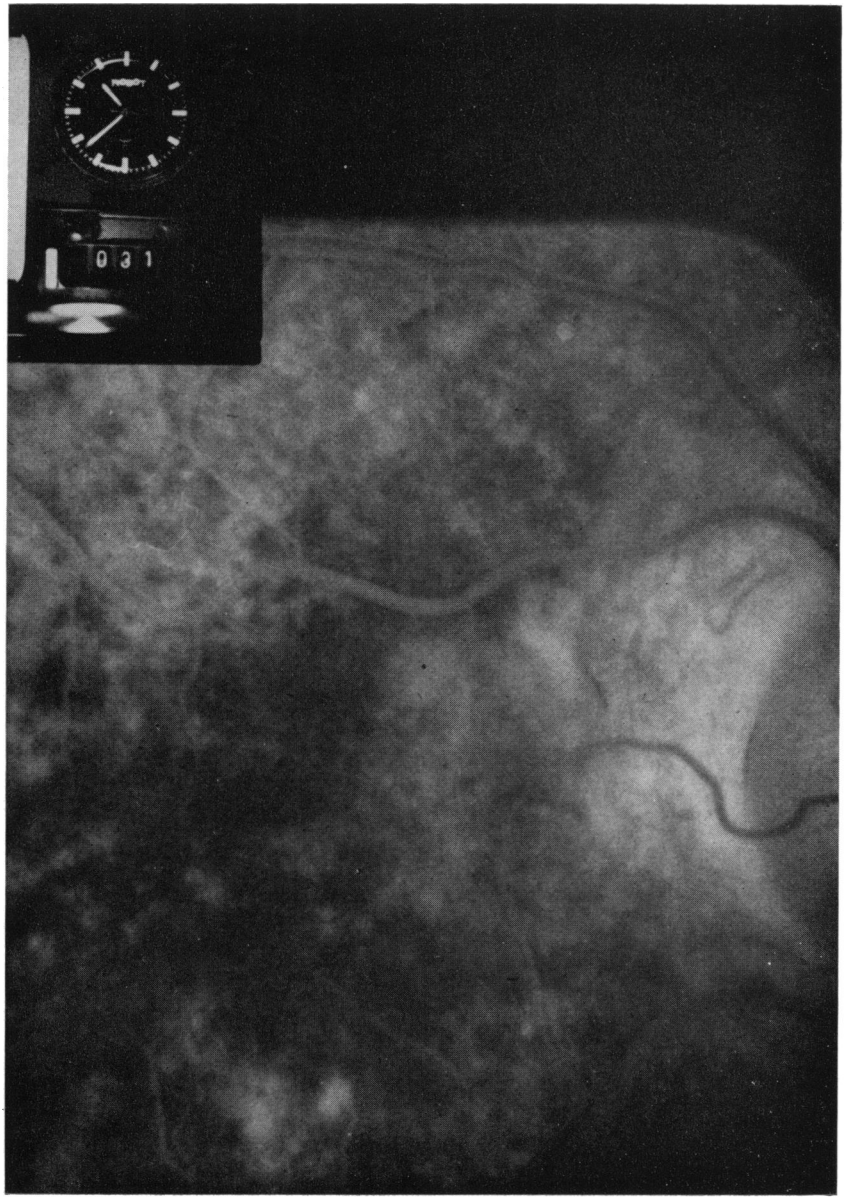

FIGURE 22
Fluorescein injection, arterial phase. Female.

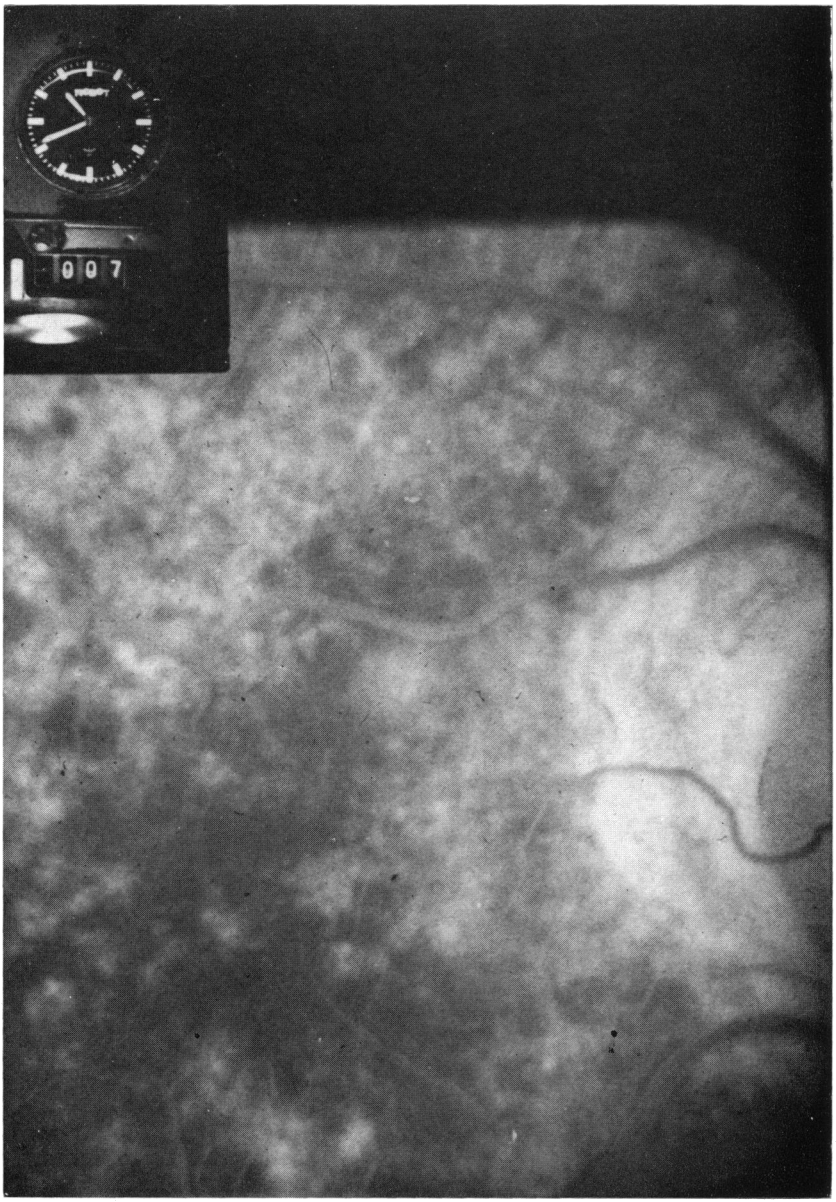

FIGURE 23
Fluorescein injection, venous phase. Same patient as in Figure 22.

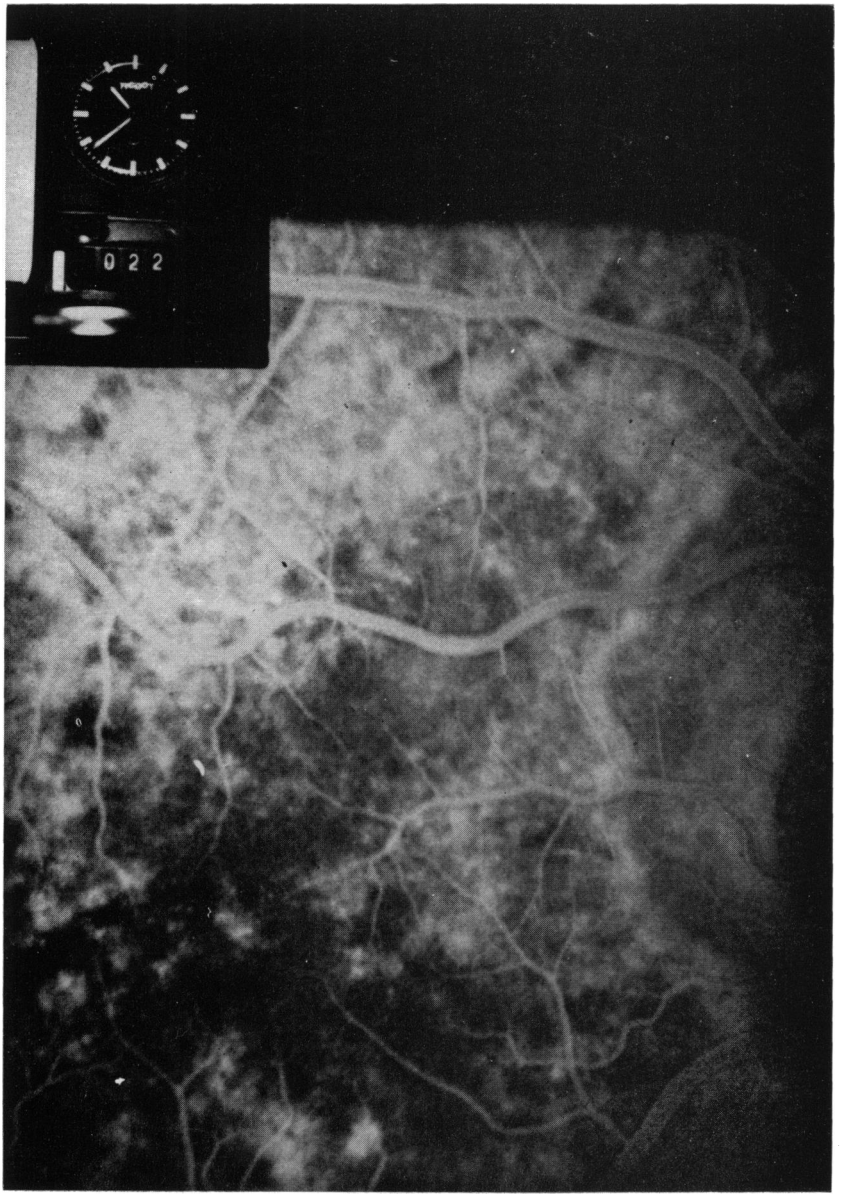

FIGURE 24
About 90 seconds after injection of fluorescein. Same patient as in Figure 22.

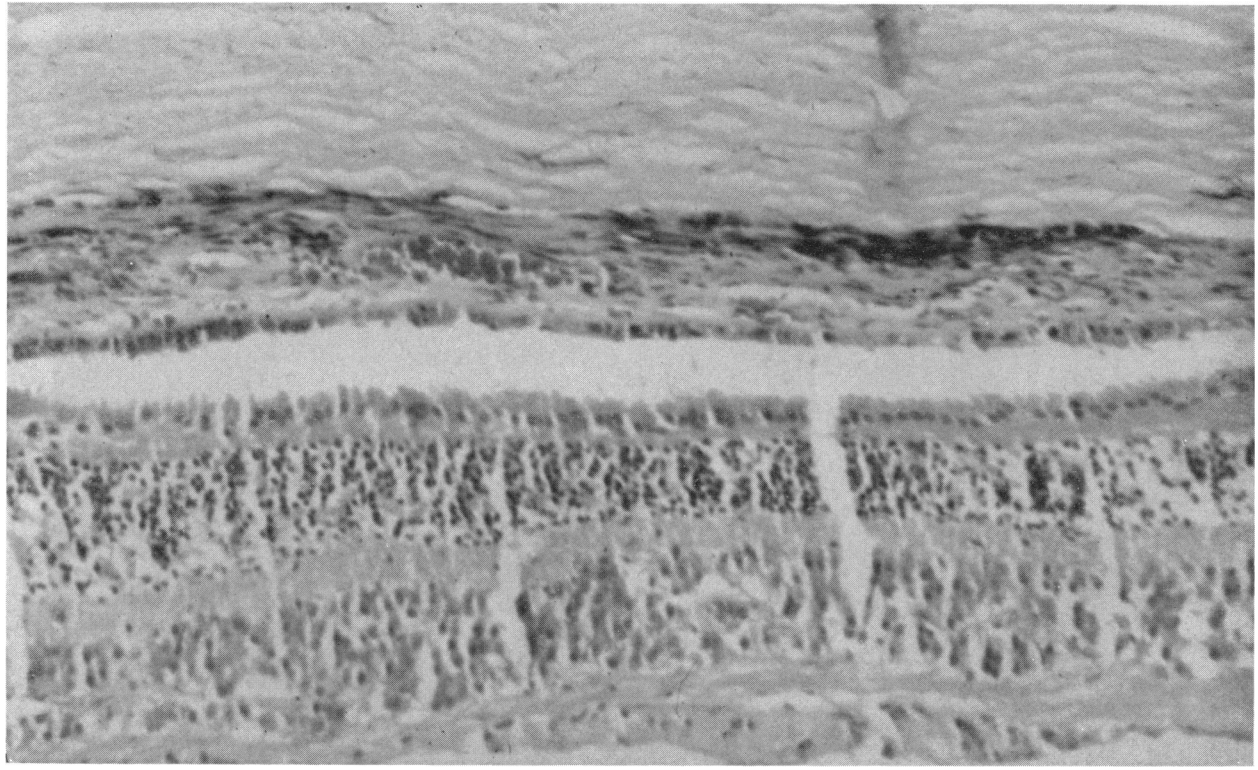

FIGURE 25
Macular region, showing some identifiable cones, choroid, pigment epithelium.

were rounded, neither rodlike nor thin and long as are normal cones at the macula. Many of the nuclei lay external to the external limiting membrane.

Cones close to the macula, taken from a section of a normal eye, are shown in Figure 26. In this section the cones are long and thin. There are a few rounded cones and an occasional nucleus lying outside the external limiting membrane between closely packed, thin, rodlike bodies of receptors. In contrast, the cones from E.P. were all rounded, many nuclei were outside the external limiting membrane, the cones were isolated with space between adjacent cones, and there were no long, thin, closely packed receptors.

CASE II.

This man was the propositus in the S family (S 3). His right eye has been described previously. He died, September 1968, at the age of 62 years. His left eye was obtained six hours after death. It was fixed in a perfumed embalming fluid of unknown composition and was not received at the laboratory until 48 hours later. Despite this, the condition of the tissues was reasonable. For the past two years of his life the patient had been able to appreciate only hand movements with central projection. His ocular pressure had been normal. He had had some posterior subcapsular lenticular opacities but it had been possible to see the fundus, which was completely white with only a trace of red color about the disk and at the macula. His karyotype was normal for both number and morphology of the chromosomes.

The anterior segment was not remarkable. The corneal epithelium was intact and of normal thickness. Bowman's membrane was present, the corneal stroma was regular, and Descemet's membrane and endothelium could be traced right across the back of the cornea. The angles were open and the trabecular structures and Schlemm's canal were not remarkable. The stroma of the iris was rather diaphanous; the pigment epithelium was somewhat atrophic. The lens showed some nuclear sclerosis and anterior and posterior subcapsular vacuoles. The ciliary body was not remarkable.

The significant changes were confined to the posterior part of the globe. The peripheral retina was atrophic; there was cystic degeneration and also loss of most of its substance. The internal limiting membrane was present and glial cells and a few nuclei from what appeared to be the inner nuclear layer remained. Bruch's membrane could not be identified. There were some small but sclerosed vessels and some fibrous strands representing choroid (Figure 27). In the equatorial region the internal limiting membrane of retina was present and thickened; some glial cells and nuclei of the inner nuclear layer were present. The choroid was missing so that the remnant of retina lay against the sclera (Figure 28). At the posterior pole the internal limiting membrane of the retina was intact, the nerve-fiber layer was atrophic; two tenuous layers of cells could be traced, appearing to be inner and outer layers; the rods and cones were missing. In places, remnants of Bruch's membrane could be traced. The choroid showed a few sclerosed vessels and some fibrous strands (Figure 29). The nerve columns of the optic nerve were shrunken and the nerve fibers were replaced with glia (Figure 30).

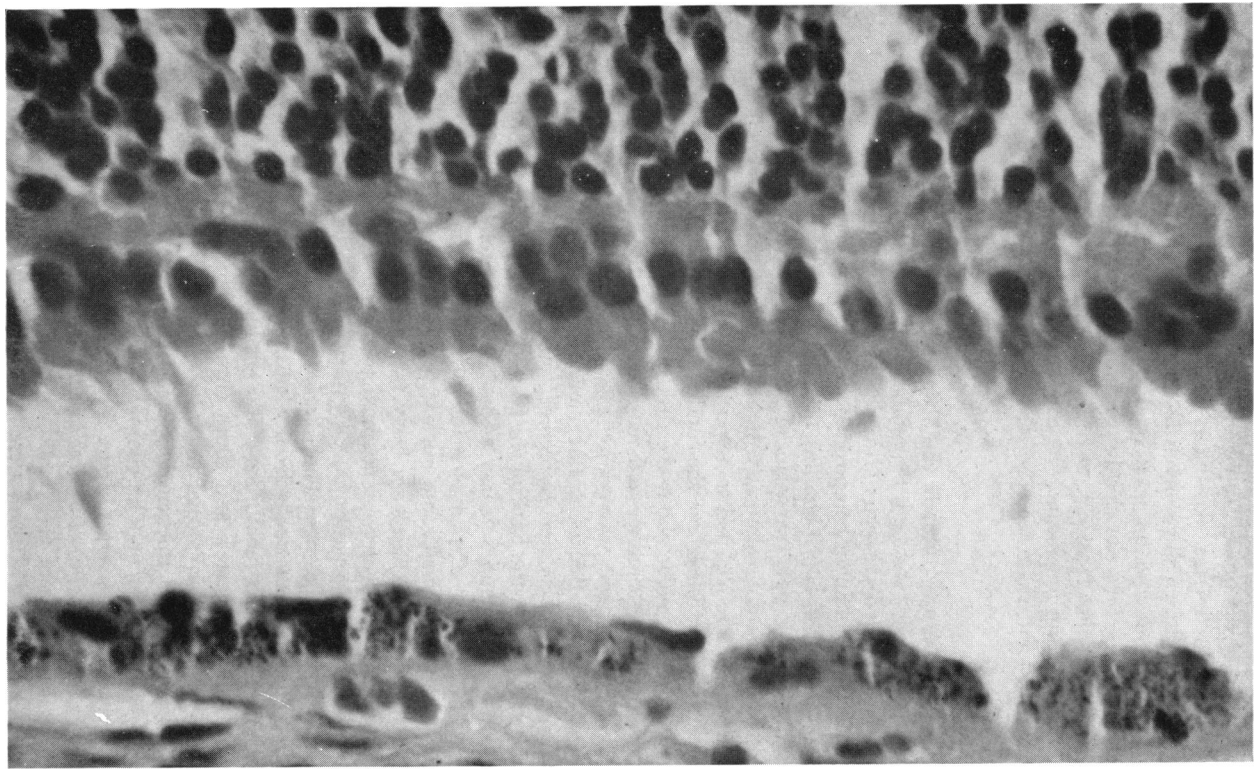

FIGURE 26
Macular region, higher power to show the stubby remnants of cones.

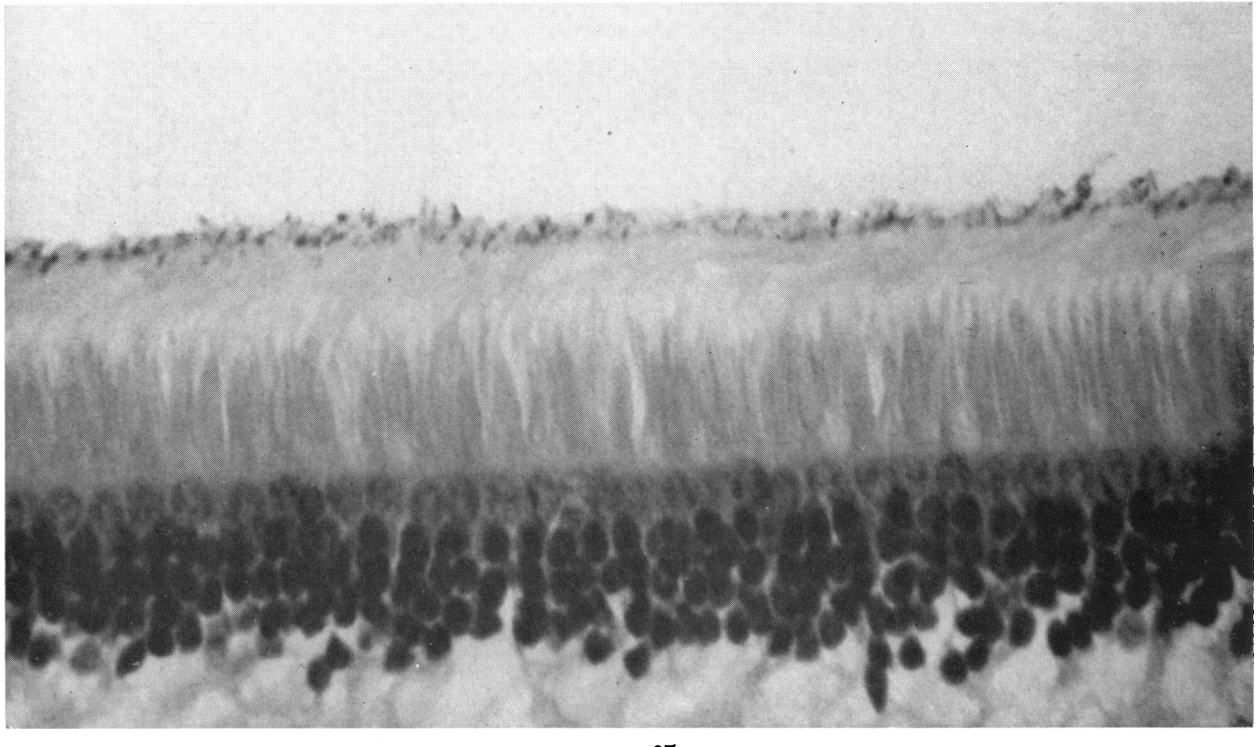

FIGURE 27
Control eye, normal macular region.

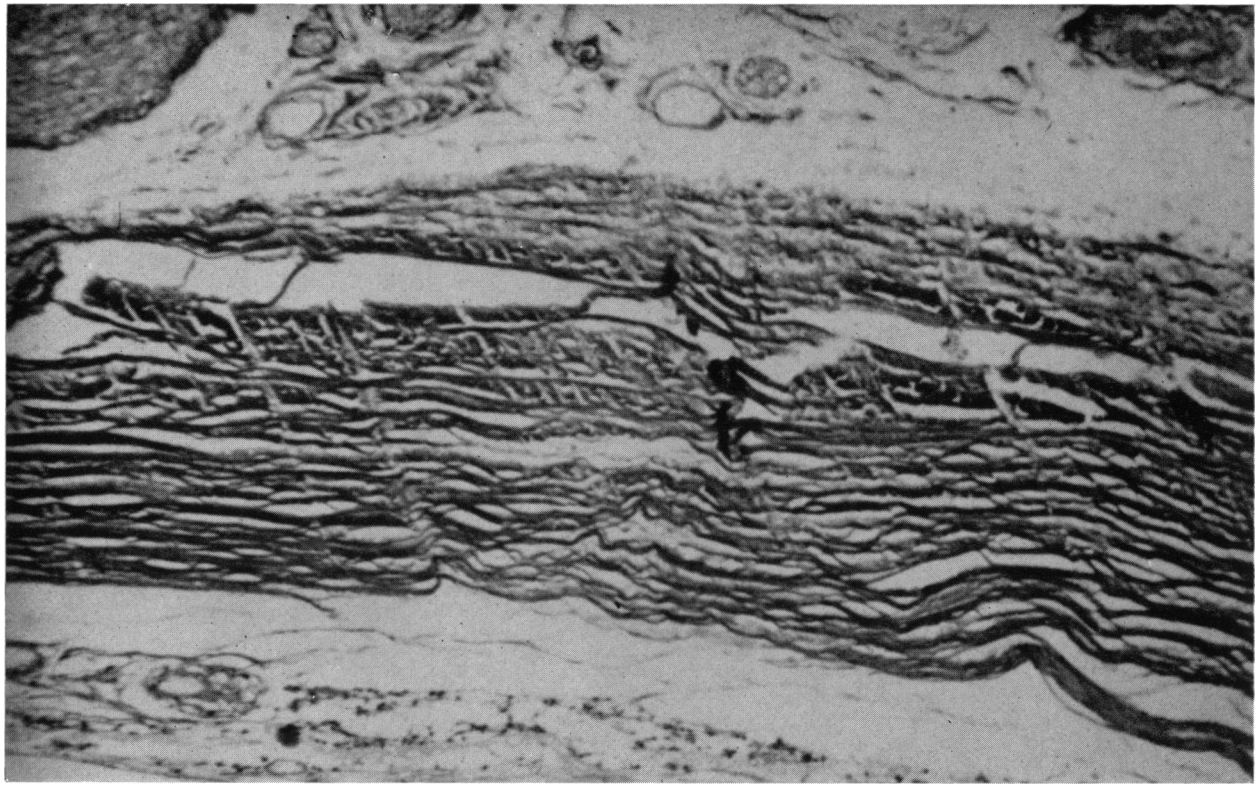

FIGURE 28
Far peripheral region of the fundus.

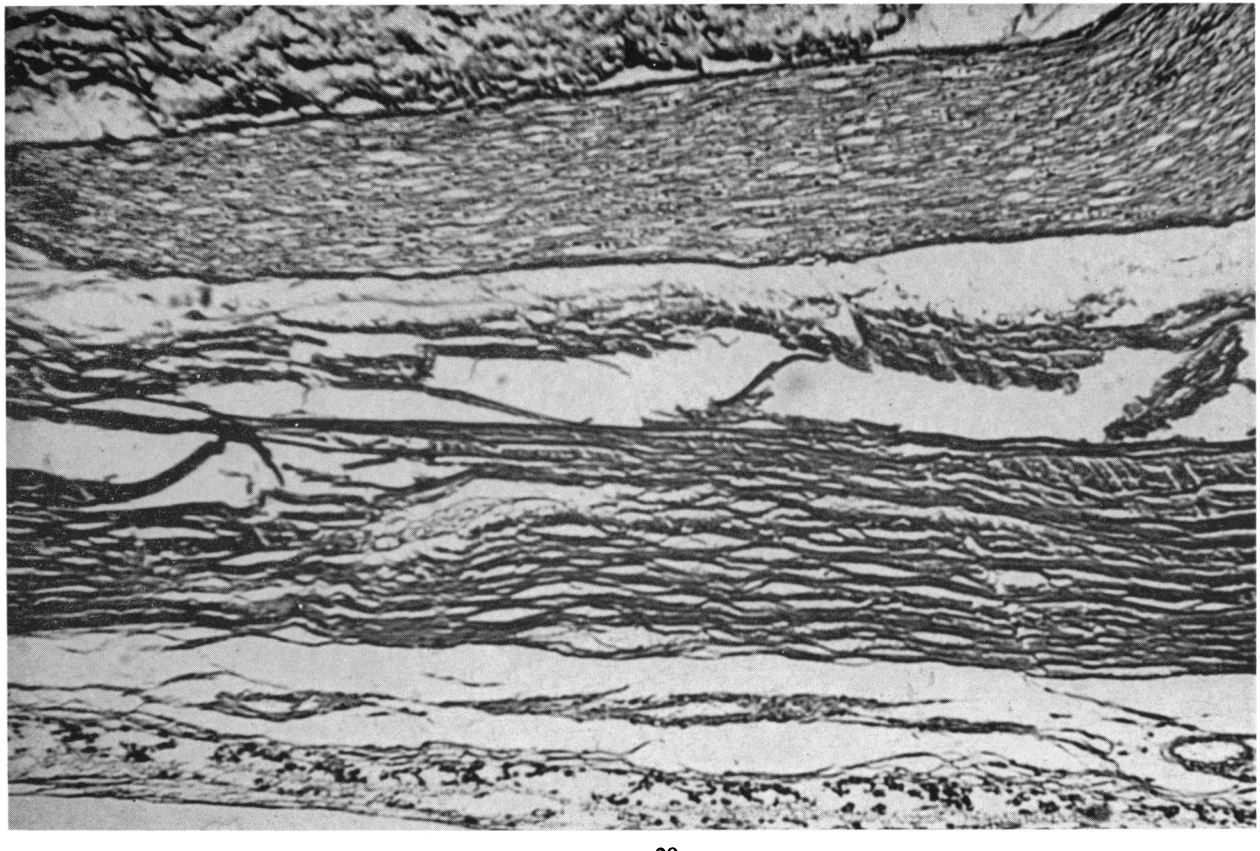

FIGURE 29
Midperipheral region of the fundus.

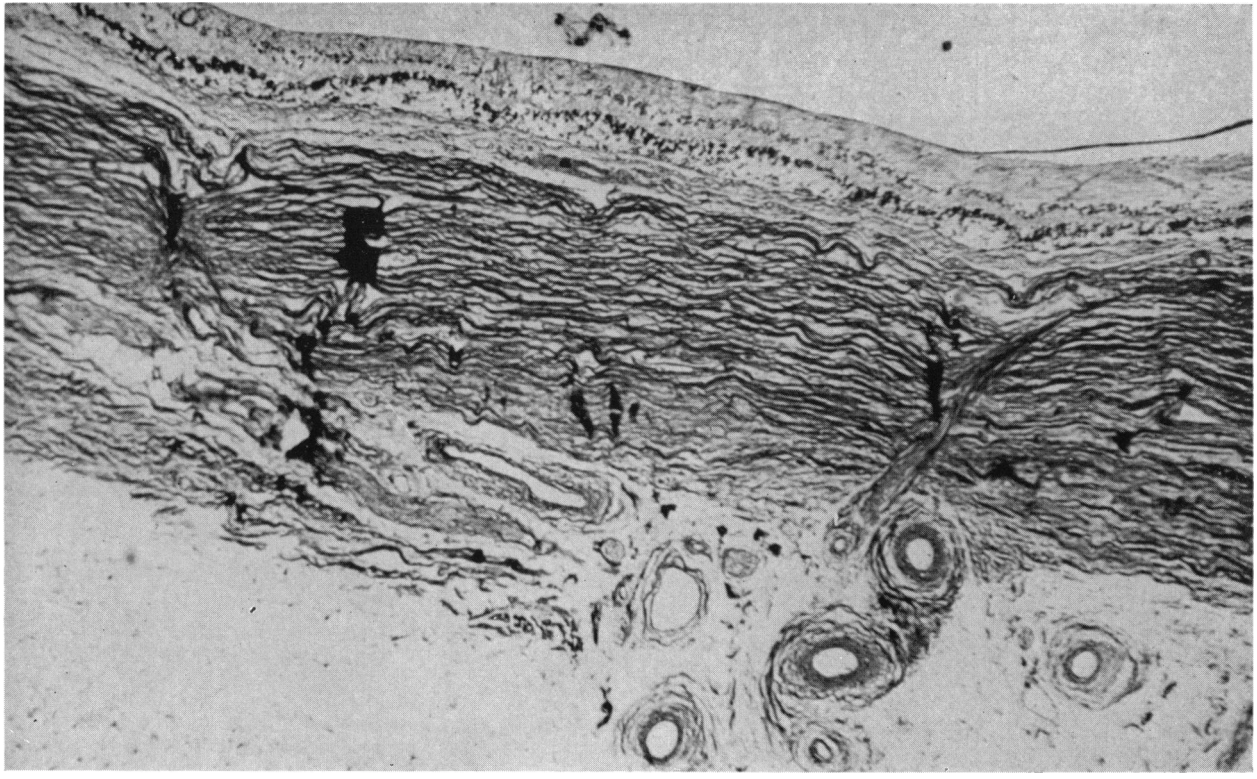

FIGURE 30
Near posterior pole of the eye, showing degenerate retina and withered choroid.

DISCUSSION

This review of the families with progressive chorioretinal atrophy, which were previously described by my father and me, confirm our earlier findings. On re-examination of these families, the original observations and conclusions can be extended.

The picture in the male is more varied than was previously realized.[7–10] A fundus in a man showing large areas of atrophy and great masses of pigment should raise the suspicion of choroideremia. Similarly, a fundus showing pigmentation and atrophy of bizarre appearance warrants consideration of choroideremia. A history of night blindness would be of help. The one thing that will decide the diagnosis is a history of other members of the family being affected and examination of members of the family.

The female may show severe changes, even as marked as in the male. However, in nearly all the cases, pigmentary disruption is present but the condition is benign.

The field defects are more varied than was previously realized.[11] In the male the initial findings are lakes of decreased sensitivity in the midperiphery. These coalesce into the most irregular and bizarre scotomas or isopters. The amalgamation of these defects leads to a midperipheral ring scotoma, which in turn breaks through to the periphery. The final central field is small and quite irregular in shape and is not necessarily exactly central in location. In the female with marked pigmentary change, midperipheral lakes of decreased sensitivity occur and with static perimetry these probably would be found.

Color vision is difficult to assess. The males and often the females showed poor color discrimination on the Farnsworth 100-hue test. Because of this it is hard to judge if there is a specific defect for blue. Tritanopia has been suggested[3] but more work would be necessary before that diagnosis could be confirmed. The affected males showed poor discrimination on the Farnsworth test. The lack of ability to read the Ishihara or Hardy-Rand-Rittler plates is probably the result of a small visual field and does not specifically indicate a defect in color sense.

The electroretinogram is extinguished in the male. This confirms the results of Bounds and Johnston.[12] This lack of electric activity occurs even when the disease is not far advanced and when there is still good acuity and a moderate field of vision. Jacobson and Stephens noted some remaining α wave but no β wave.[13] On this I cannot

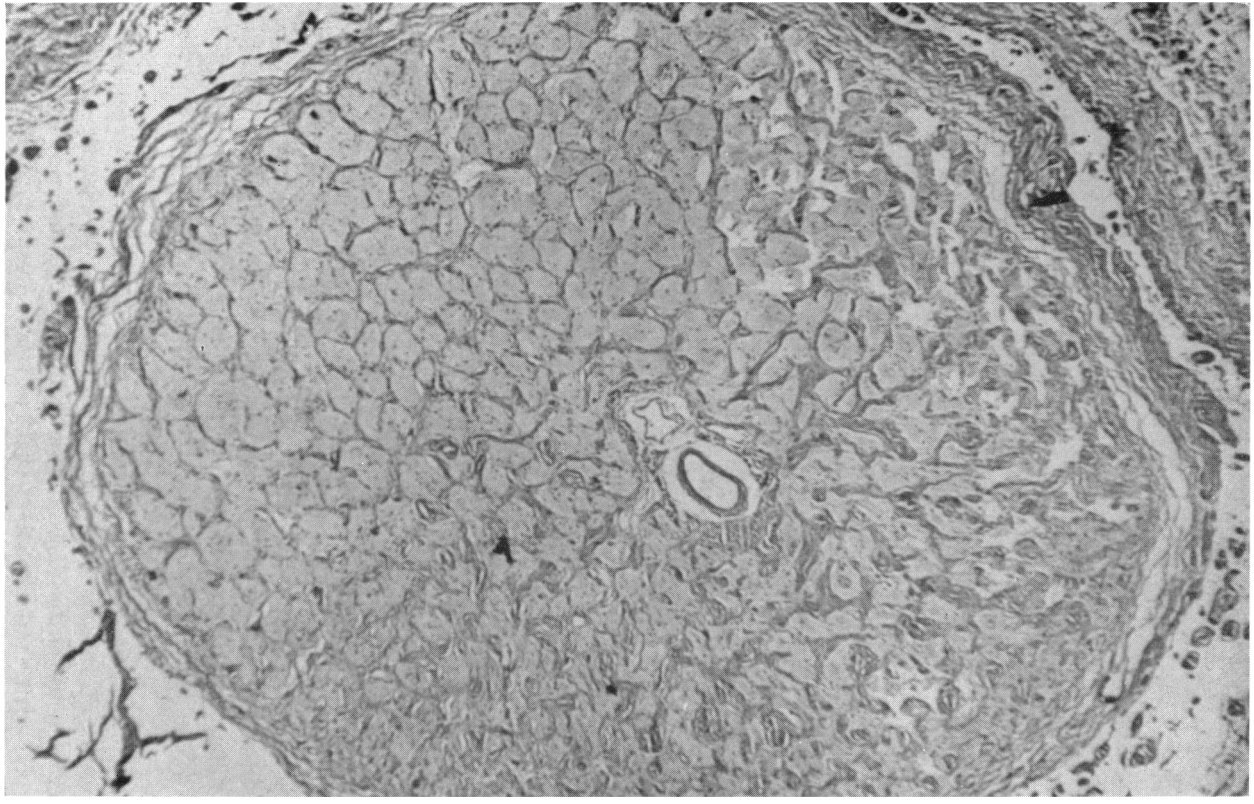

FIGURE 31
Optic nerve showing extensive atrophy.

comment. However, there seems to be a rather specific, or selective, effect extinguishing the retinogram.

The chance observation that, in the young male, after 45 minutes there is a late improvement in scotopic sensitivity is worthy of comment. There would seem to be a slowing in the regeneration of night vision. Apparently night vision can return but the process is delayed.

The pathologic findings in the 43-year-old male point to a selective loss of the outer segments of the cones and, presumably, the rods. The disease is of a nature that leads to degeneration of the outer segments of the visual cells.[14] The fact that death of the pigment epithelium is a prominent feature of the disease places the primary defect right in the region of outer rod segments and pigment epithelium. The fact that there is no other systemic abnormality occurring in these patients[11] indicates that the enzymatic defect must be very specific indeed.

CONCLUSION

In a family of about 1600 descendants from a man with choroideremia, many are affected with the same disease, some being men with blindness and others being women with a pigmentary stigma in the fundus. The males show loss of the outer layers of the retina, the pigment epithelium, and choroid. The disease continues unabated in the family. The steady progress of the disease and the peculiar location of the changes are unique and invite speculation as to the primary metabolic defect that must be present.

ACKNOWLEDGMENT

I would like to thank the many people who helped gather these data, particularly Dr. Lois Lloyd, Dr. Michael Shea, Dr. W. S. Hunter, Dr. P. K. Basu, and the technical staff of the Department.

APPENDIX

FAMILY RL

RL III – 43

This patient has no visual complaints. There are very mild changes in the midperiphery. There is some atrophy with areas of paleness and very little pigment, less than was recorded 23 years ago.[1] There is a nuclear cataract in the right eye. She reads print with either eye. The iris is hazel.

RL IV – 14

Born in 1907, this patient has no visual symptoms. The picture in the fundi is as we previously described,[1] except that there now is an area of atrophy about the disks. There is some speckling of pigment at the maculae. The disks, vessels, vitreous, and lenses are normal. Color vision is normal with the Ishihara plates. Manifest refraction is: o.d., +1.00 +0.50 × 10 = 20/20; o.s., +1.00 +0.50 × 170 = 20/20. The fields are full to 3/1000 white test object. The iris is gray.

RL IV – 29

Born in 1897, this patient has no visual complaints. Correction is: o.d., +3.50 +0.50 × 180; o.s., +3.50. She can read fine print with either eye. There are mild changes across the midperiphery of both fundi. There are many small clusters of squared pieces of pigment and small areas of yellow glow of light coming through from the sclera. The disks, vitreous, and lenses are normal. The iris is brown.

RL IV – 30

Born in 1899, this patient has no visual complaints. There are very mild changes only in limited sectors of both fundi, consisting of squared chunks of pigment and areas of yellow translucence. Visual acuity is: o.d., 20/20; o.s., 20/20. The fields are full to a white headed pin. The iris is olive. Color vision is normal using the Ishihara plates.

RL IV – 39

This patient was born in 1900. She feels that she is not as sure of herself at night as she was when younger. The fundi are very similar to what we described 23 years ago,[1] showing a lot of baring of sclera and scattered pigment. There is a ring of choroidal thinning about the disks. The disks, vitreous, and lenses are normal. Correction is: o.d., +3.00; o.s., +3.00. Color vision is normal using the Ishihara plates. The iris is gray.

RL IV – 42

Born in 1916, this patient has considered herself blind at night for the last ten years. The fundi show the most marked changes I have ever seen in a female. There is a ball of pigment collected at each macula. The midperipheral area is almost all white, presumably due to loss of pigment epithelium and choroid. There is red color in the periphery and pigment is scattered in and on the retina, right across the fundi. About the disk the choroid is thin. She wears correction: o.d., +2.00 −0.75 × 90 = 20/20; o.s., +1.50 −0.50 × 90 = 20/20. Using a small pin and local arrangements, she has midperipheral defects to a 4/1000 white test object in a band 20–40° from fixation. The disks are pale, the vitreous, lenses are normal. Color vision is normal with the Ishihara plates but discrimination is poor on the Farnsworth 100-hue test. The iris is gray.

RL V – 19

This patient was born in 1918. She does not feel sure at night but has no other ocular complaints. She has had carcinoma of the cervix and of the right breast. Under Cyclogyl refraction is: o.d., +4.00 +0.75 × 105 = 20/30; o.s., +4.50 +0.75 × 135 = 20/20. The fields are full to 3/1000 white test object. She had the typical mild female changes in her fundi. There are chunks of pigment in the midperiphery. There are patches of pale translucence in the periphery and about the disk. The disk, vitreous, and lens are normal. Color vision is normal with the Ishihara plates.

RL V – 20

Born in 1922, this patient has no visual complaints. There is some atrophy about the disks. In the midperiphery are areas of scattered pigment with accompanying pale regions. The vitreous is clear; the disks, retinal vessels, and lenses are normal. Visual acuity is: o.d., 20/20; o.s., 20/20. The fields to 1/1000 and 1/330 white test objects are normal. The dark-adaptation curve is normal. There is average discrimination with the Farnsworth 100-hue test.

RL V – 29 *RL V – 73*

Born in 1936, this patient has no visual symptoms. There are areas of scattered pigment and atrophy in the midperiphery. Pigment is aggregated at the maculae. The disks, vessels, vitreous, and lenses are normal. Manifest refraction is: o.d., +0.75 × 60 = 20/20; o.s., +0.75 × 120 = 20/20. The fields are full to a 3/1000 white test object.

RL V – 65

This patient was born in 1920. He was first seen in 1953. He has noted some difficulty at night for 10 years. In the last three years he has tended to bump into things. Manifest refraction is: o.d., −0.75 −0.50 × 85 = 20/20; o.s., −0.25 −0.75 × 70 = count fingers. There are huge areas of gross disruption of pigment and of bared sclera across both fundi. The disks are pale. The retinal vessels are of normal size. The left macula shows a pattern of choroidal sclerosis. The right macula has a normal red color. The fields are 15° across using a 3/1000 white test object before either eye.

RL V – 66

Born in 1935, this patient has no visual complaints. She can read fine print with either eye. There are mild pigmentary changes, with some atrophy in the midperiphery only. The iris is hazel. The appearance is similar to that of her mother.

RL V – 77

Born in 1936, this patient has no visual complaints. There are only mild pigmentary changes in the periphery. The pigment is grouped and chunky,

and there are neighboring pale areas. The disks, vitreous, and lenses are normal. Correction is: o.d., +2.00; o.s., +2.00. She can read fine print with either eye. The iris is gray.

RL V – 80

Born in 1933, this patient has no visual complaints. There are very mild changes in the midperiphery of both fundi. These are hard to find; they give the appearance of pigmentary breaks along the directions of the retinal blood vessels. The vitreous, disks, and lenses are normal. Color vision is normal using the Ishihara plates. The iris is brown. Correction is: o.d., +2.00 +0.50 × 90; o.s., +2.00 +0.50 × 90. She can read fine print with either eye.

RL V – 85

Born in 1932, this patient has no visual complaints. There are a limited number of patches of dispersed pigment and choroidal thinning in the midperiphery. The region of the disk and macula is normal. She can read fine print with either eye. The iris is hazel.

RL V – 91

Born in 1929, this patient has no visual complaints. There is moderate atrophy in the midperiphery, with an accompanying yellow glow from the choroid. Squared chunks of pigment are distributed in patches across the fundi. The disks, vitreous, and lenses are clear. She can read fine print with either eye. Correction is: o.d., +1.00 +1.00 × 90; o.s., +1.00 +1.00 × 90.

RL IV – 18

Born in 1948, this patient has no ocular complaints. She has had a divergent squint all her life. This is an alternating exotropia of 50 diopters with overaction of both inferior obliques. Manifest refraction is: o.d., +3.00 +1.00 × 60 = 20/20; o.s., +3.00 +0.75 × 180 = 20/20. The fields are full to 3/1000 white. She has the typical pigment of a carrier, much as has her mother. There is no accumulation of pigment at the macula. Color vision is normal using the Ishihara plates.

RL VI – 19

Born in 1949, this patient has no ocular complaints. The changes in her fundi are marked. There are squared chunks of pigment all across the midperiphery; neighboring these are areas of yellow reflex at least as large as the disk. The macular area is clear. There is some thinning of choroid about the disks. The disks, vessels, vitreous, and lenses are normal. The fields are full to 3/1000 white. Manifest refraction is: o.d., +0.50 × 90 = 20/20; o.s., −0.75 = 20/20. Color vision is normal using the Ishihara plates.

RL VI – 38 *RL VI – 96*

Born in 1958, this patient has no visual complaints. There is some atrophy about the disks. There is diffuse, fine speckling of pigment in the midperiphery and far periphery of both eyes. The disk and macular areas are clear. The disks, vessels, vitreous, and lenses are normal. Manifest refraction is: o.d., −0.75 = 20/20; o.s., −0.75 = 20/20. Color vision is normal using the Ishihara plates. The fields are full to a 3/1000 white object. The iris is blue.

RL VI – 39 *RL VI – 97*

This patient was born in 1960. There is marked atrophy about the disks. There is gross pigmentation in the midperiphery with large areas of pale sclera showing through. There is a heavy ball of pigment collected at each macula. Disks, vessels, vitreous, and lenses are normal. Color vision is normal using the Ishihara plates. The iris is brown. Manifest refraction is: o.d., +0.00 = 20/20; o.s., +0.50 = 20/20.

RL VI – 40 *RL VI – 98*

This patient was born in 1964. There is marked pigmentation in the periphery in both fundi. This is dark and heavy, with a few neighboring small yellow areas. About the disk and macula there are some pigmentary granules but the region is intact. The disk, vessels, vitreous, and lens are clear.

RL VI – 93

This patient was born in 1962. There is moderate atrophy of the pigment epithelium with scattered particles of pigment all across both fundi. There is thinning of choroid about the disks and the disks, vessels, vitreous, and lenses are normal. This is a much more severe change than is shown by her mother.

RL VI – 108

Born in 1953, this patient has always had difficulty in the dark. Recently he has had to be careful during the day. There is diffuse scattering of pigment in large chunks in all the middle zones of the fundus. There is very little scleral baring. The disks, lenses, and vitreous are normal. Visual acuity is: o.d., 20/20; o.s., 20/20. The fields are full to a white headed pin. The iris is gray-brown. Color vision is normal using the Ishihara plates.

RL VI – 109

Born in 1959, this patient has difficulty seeing at night. There is considerable baring of sclera in all of the midperiphery. There is a lot of irregular pigment lying in the far periphery and there is a ring of pigment collected about the disk. Visual acuity is: o.d., 20/20; o.s., 20/20. The iris is gray. Color vision is normal, using the Ishihara plates.

RL VI – 120

Born in 1951, this patient has difficulty seeing at night but is quite capable during the day about the farm. Great masses of pigment are present in the midperiphery in both fundi. There are accompanying pale areas and the choroid is thin about the disks. The disks, vitreous, and lenses are normal. The fields are full to a white-headed pin. Visual acuity is: o.d., 20/20; o.s., 20/20. The iris is brown.

RL VI – 122

Born in 1955, this patient is blind at night, careful when going about during the day. There are large areas of atrophy, particularly in the midperiphery and about the disks. There are scattered strands of pigment in and on the retina. There is an island of red color at the macula, with choroidal vessels extending from the disk. There are also irregular islands of red color in the far periphery. The vitreous, disks, and lenses are normal. The iris is hazel. Color vision is normal using the Ishihara plates. Correction for both eyes is $+1.00$ $+1.00 \times 180$. He can read fine print with either eye.

RL VI – 131

Born in 1962, this patient has good vision according to her mother. There are marked pigmentary changes about the disk, midperiphery, and far periphery of either eye. The choroid is thin about the disks. The disks, vitreous, and lenses are clear. She can read book print with either eye. These changes are much more marked than are those of her mother.

RL VI – 141

This patient was born in 1954. Her findings, very much like her mother, show moderate change.

RL VI – 142

Born in 1952, this patient has no visual complaints. She has an area of choroidal atrophy about the disks. The midperiphery shows large blocks of pigment on and in the retina and large, irregular, pale orange-yellow areas of translucence. The disks, maculae, vitreous, and lenses are normal. She can read fine print with either eye. Color vision is normal using the Ishihara plates.

RL VI – 143

Born in 1954, this patient has no visual complaints. The changes in the fundi are even more marked than in her sister. There are large masses of broken pigment, big irregular aeas of translucence. Lenses, vitreous, and disks are normal. Color vision is normal using the Ishihara plates. She can read fine print with either eye. Correction is: o.d., $+1.50$; o.s., $+2.00$. The iris is olive.

RL VI – 144

Born in 1954, this patient has had difficulty seeing at night ever since he can remember. There is thinning of the choroid about the disk. The fundus is pale, the bare sclera showing except about the disk, macula, and in the far periphery. There are marked collections of pigment, widely scattered, but particularly neighboring the macula. Manifest refraction is: o.d., −0.50 = 20/20; o.s., −0.50 = 20/20. The disks, vitreous, and lenses are clear. The field is 20° to 2/1000 white test object.

RL VI – 145

Born in 1957, this patient is bothered by bright light, but otherwise has no complaints. There is some thinning of choroid, with pallor about the disks. In the midperiphery there are multiple small pale areas, with a yellow glow coming through from the sclera. Clumps of pigment are dispersed in an irregular pattern across most of the fundi. The region of the macula and of the far periphery shows a normal red color. Visual acuity is: o.d., 20/15; o.s., 20/15. The fields are 35° from fixation to 2/1000 white test object.

FAMILY S

S II – 3

Born in 1903, this patient now is industrially blind. The fundi are almost completely atrophic and white. There is a small area of red about the disks and a few vessels extending into an island of red color at the macula. The disks are pale; the retinal vessels are normal. The vitreous and lens are clear. Visual acuity is: o.d., 20/120; o.s., light perception, no projection. Retinoscopy showed: o.d., −3.00 +0.50 × 180; o.s., −2.50. The field of the right eye is 2° for a 5/1000 white test object. He could not read the Ishihara color vision plates. The iris is blue. There is a photopic curve in the first 15 minutes of dark adaptation with no scotopic component. His karyotype was not obtained due to extreme clumping of cells in tissue culture.

S II – 7

Born in 1911, this patient has been night blind since the age of 17 years. He has a divergent squint with the right eye fixing. The right fundus is white with an island of red color about the disk and extending to the macula. The left fundus is white. Manifest refraction is: o.d., −6.50 +1.00 × 55 = 20/60; o.s., −5.00 +1.90 × 90 = no light perception. The field is 2° to 3/1000 white test object. He shows low discrimination on the Farnsworth 100-hue test. He could not reach the scotopic range with the adaptometer. The karyotype is normal.

S II – 9

Born in 1916, this patient has no visual complaints and no loss of night

vision. Her fundi are as they were described previously.[1] Visual acuity is: o.d., 20/20; o.s., 20/20. Fields to 3/1000 and 3/330 white test objects are full. The electroretinogram has an intact curve. The dark-adaptation curve is normal. Color vision is normal using the Farnsworth 100-hue test. The karyotype is normal. The iris is brown.

S III – 5

Born in 1925, this patient was last seen in 1956. She had been followed since 1946. She had no visual complaints. She showed mild pigmentary changes in both fundi. Manifest refraction is: o.d., +2.25 −0.50 × 180 = 20/20; o.s., +2.25 −0.75 × 180 = 20/20. She has been deaf ever since she had meningitis as a child.

S III – 6

Born in 1941, this patient has no visual complaints. There are salt and pepper chunks of pigment all across the fundi. Between are pale areas, yellow in color. There is some choroidal thinning about the disks; the maculae are clear. Disks, vitreous, and lenses are all normal. Correction is: o.d., +1.50 +0.75 × 90 = 20/20; o.s., 20/20. The fields are normal to 3/330 white, 5/1000 blue, 5/1000 red test objects. Color vision is normal with the Ishihara plates. The iris is blue.

S III – 8

Born in 1940, this patient has no visual complaints. Moderate pigmentary changes are present. Pigment clumps lie in all quadrants of both fundi. The choroid is thin about the disk. The region of macula is normal and the disks, vessels, vitreous, and lenses are normal. She achieves average color discrimination with the Farnsworth 100-hue test. The fields are full to 2/1000 white test object. Manifest refraction is: o.d., +0.50 × 45 = 20/20; o.s., +0.00 = 20/20. The iris is brown. This patient has been followed for 12 years with no change.

S III – 17

Born in 1938, this patient has no visual complaints. She shows moderate pigmentary disruption across both fundi. This is about as described earlier.[1] The fine pigmentation at the macula has disappeared. Manifest refraction is: o.d., +1.00 = 20/20; o.s., +0.50 +1.50 × 180 = 20/20. Color vision is normal using the Farnsworth 100-hue test. Fields are full to 3/330 white and 3/1000 white test objects. The dark-adaptation curve is normal. The karyotype is normal.

SS III – 18

Born in 1940, this patient is working as an artist, but cannot get about at night. He was last seen in 1962. Manifest refraction is: o.d., −0.50 +1.00 × 150 = 20/50; o.s., −0.50 +1.00 × 30 = 20/40. The fundi have

become pale. Choroidal vessels are still visible but there are large areas of atrophy. The macular area and far periphery are still red. The karyotype is normal.

S IV – 6

Born in 1960, this patient is reluctant to go out at night. He shows severe pigmentary changes in both fundi. There are heavy masses of pigment scattered irregularly, with a few atrophic pale areas between. There is a sprinkling of pigment at the macula. Under Cyclogyl, refraction is: o.d., +2.50 = 20/20; o.s., +2.00 = 20/20. Fields are full to 3/1000 white test object. There is poor color discrimination on the Farnsworth 100-hue test. The iris is brown.

S IV – 7

Born in 1961, this patient has no visual complaints. There is thinning of choroid about both disks and mild speckling all across both fundi but more marked in one quadrant of each eye. Pigment is collected at the maculae. The disks, retinal vessels, and lenses are normal. Visual acuity is: o.d., 20/20; o.s., 20/20. There is poor color discrimination with the Farnsworth 100-hue test. The iris is brown. The fields are full to 2/1000 white test object. This patient was seen in 1961 and 1969; the appearance did not change between examinations.

FAMILY K

K I – 1

This patient was normal on examination.

K I – 2

Born in 1922, this patient has no visual complaints. In several patches in the mid- and far peripheries of each eye there are clusters of chunks of pigment. In these regions, the choroid is thin and a yellow glow comes through. The disks, vessels, vitreous, and lenses are normal. Visual acuity is: o.d., 20/20; o.s., 20/20. Fields full by confrontation with a white headed pin.

K II – 1

Born in 1945, this patient bumps into things during the day. Color vision using the Ishihara book is slow but correct, but discrimination is poor as recorded on the Farnsworth 100-hue test. The dark-adaptation curve remains at the photopic level. Under Cyclogyl, refraction is: o.d., −3.50 +3.00 × 90 = 20/120; o.s., −3.50 +3.00 × 90 =20/80. There is marked diffuse disruption of pigment, which lies in large blocks in and on the retina. There are large irregular areas where the white of sclera shows. There is an intraretinal disk of pigment at each macula. The disks and

retinal vessels are normal. There are pigment granules scattered in the vitreous. The lens is clear. There is a midperipheral ring scotoma with object IV, intensity 3 of the Goldmann perimeter.

K II – 2

Born in 1946, this patient has no visual complaints. There are large blocks and masses of pigment all across the fundi but these are concentrated in the midperiphery. There are innumerable pale yellow areas among the pigment. The disks, vessels, and vitreous are clear. Fields are full to 5/330 white test object. Manifest refraction is: o.d., +1.00 = 20/20; o.s., +1.00 = 20/20.

K II – 3

This patient was normal on examination.

K II – 4

Born in 1955, this patient has noted inability to see at night, but there is no defect during the day. The fundi show atrophy about the disk, with thin choroid and exposed sclera. In the periphery there are large areas of white or yellow sclera and much broken, chunky pigment. The lens, vitreous, and retinal vessels are normal. Under Cyclogyl, refraction is: o.d., +1.00 +1.00 × 90 = 20/20; o.s., +0.75 +1.25 × 85 = 20/20. There is a midperipheral ring scotoma with object III intensity 3 of the Goldmann perimeter. There is poor color discrimination using the Farnsworth 100-hue test. Dark adaptation using the Goldmann-Weekers adaptometer reaches only to the photopic level.

K II – 5

Born in 1963, this patient has no visual complaints. There are some peripheral pale areas with accompanying chunky masses of pigment. The whole area about the disk and macula is normal. Under Cyclogyl, refraction is: o.d., +1.50 +2.00 × 95 = 20/20; o.s., +1.00 +1.50 × 90 = 20/20.

REFERENCES

1. McCulloch, C., and R. J. P. McCulloch, A hereditary and clinical study of choroideremia, Tr. Am. Acad. Ophth., 52:160–90, 1948.
2. Harris, G. S., and J. R. Miller, Choroideremia, visual defects in a heterozygote, A.M.A. Arch. Ophth., 80:423–9, 1968.
3. Fraser, G. R., and A. I. Friedman, Choroideremia in a female, Brit. M. J., 1:732–4, 1968.
4. Jaeger, W., and P. Grutzner, Der Funktionverfall bei progressiver tapetochoroidealer Degeneration (Choroideremia), Ophthalmologica, 143:305–11, 1962.
5. McCulloch, C., The pathologic findings in two cases of choroideremia, Tr. Am. Acad. Ophth., 56:565–72, 1950.
6. Rafuse, E. V., and C. McCulloch, Choroideremia, a pathologic report, Canad. J. Ophth., 3:347–52, 1968.

7. Fornes Peris, E., Hallazgo y estudio-histopatologico de an caso de coroideremia, A.M.A. Arch. Ophth., 41:356, 1947.
8. Sorsby, A., A Franceschetti, R. Joseph, and J. B. Davey, Choroideremia, clinical and genetic aspects, Brit. J. Ophth., 36:547–81, 1952.
9. Rubin, M. L., R. S. Fishman, and R. A. McKay, Choroideremia, study of a family and review of the literature, A.M.A. Arch. Ophth., 76:563–74, 1966 (color photos).
10. Goodman, G., H. Ripps, and I. M. Siegel, Sex-linked ocular disorders: trait expressivity in male and carrier females [8 yr. old ♂ poor ERG], A.M.A. Arch. Ophth., 73:387–98, 1965.
11. Kurstjens, J. H., Choroideremia and gyrate atrophy of the choroid and retina, Docum. Ophth., 19:1, 1965.
12. Bounds, G. H., and T. L. Johnston, The electroretinogram in choroideremia, Am. J. Ophth., 39:166–70, 1955.
13. Jacobson, J. H., and G. Stephens, Hereditary chorioretinal degeneration, A.M.A. Arch. Ophth., 67:321–35, 1962.
14. Grignole, A., N. Orzalesi, and G. A. Calabria, Studies on the fine structure and the rhodopsin cycle of the rabbit retina in experimental degeneration induced by sodium iodate, Exper. Eye Res., 5:86–97, 1966.

DISCUSSION

DR. GEORGE N. WISE. The original report on choroideremia in 1948 by Dr. McCulloch and his late father and this extensive follow-up of those cases 23 years later together constitute a classic on this subject. There is very little one can add, and it is equally hard to formulate a question.

The author queries the failure of choroidal fluorescence as was demonstrated in his case of choroideremia tested by fluorescein angiography. There is a simple explanation for this. Fluorescein normally leaks only from the choriocapillaris, not from larger choroidal vessels. The absence of the choriocapillaris at this stage of the disease would therefore preclude choroidal fluorescein leakage.

Although it was not stressed in the presentation, two carrier females demonstrated some loss of their peripheral visual fields. Pameyer, Waardenburg, and Henkes reported several carriers with defective dark adaption and electroretinograms. Among Kurstjens' 61 carriers, several showed various functional defects and one had a completely normal fundus at repeated examinations. Krill in 1967 and Fraser and Friedman in 1968 have both reported carriers with varying degrees of functional defect. According to Mary Lyon's hypothesis, female carriers may on rare occasion show the full disease, various lesser degrees of defect, or even an entirely normal fundus. It is worth emphasizing, therefore, that progressive functional choroideremia can appear in the female carrier, although its occurrence is rare.

In reviewing this paper one interesting sidelight came to mind. What is the explanation for the retinal arteriolar narrowing and wall hyalinization in the late stages of night-blinding retinitis pigmentosa and for the normal

retinal arterioles in the late stages of night-blinding choroideremia? Is the former due directly to the faulty gene or is there some other explanation?

Noell and his students, Dantzker and Gerstein, have studied the retinal vasculature in rats with hereditary visual-cell degeneration and in animal retinas exposed to high intensity light and iodoacetate poisoning. The fact that the same retinal vascular changes occurred in the light and poisoning experiments as were seen in the hereditary rat disease seemed to exclude a genetic effect. These workers suggested that the vaso-obliterative effect on numbers of retinal capillaries and the arteriolar narrowing could arise from the increased oxygen tension to which the inner retina was exposed. In all of the experimental conditions the rods and cones, outer nuclear layer, and outer plexiform layer disappear and a normal or slightly thinner inner nuclear layer lies adjacent to Bruch's membrane or pigment epithelial cells. With this loss of outer retina, inner retinal layers are now physically closer to the choriocapillaris and many retinal cells, previously utilizing choroidal oxygen, are no longer present. Under these conditions the inner retinal elements sustain prolonged exposure to a higher than normal gradient of tissue oxygen supplied by the unaffected choroid. This could account for the narrowing of retinal arterioles late in retinitis pigmentosa.

In further support of this hypothesis is the absence of such retinal arteriolar narrowing late in choroideremia. In this disease one has the same loss of outer retinal elements as in retinitis pigmentosa, but in addition there is loss of the choroid. Under these circumstances, the oxygen tissue gradient in the inner retina, if changed, would be lower than normal because of the absent choroid, and no oxygen narrowing of retinal arterioles would be expected.

DR. HAROLD F. FALLS. I would like to discuss two features of this paper; first, Mary Lyon's hypothesis.

As you all know, the female has two x chromosomes and the male has an x and a y chromosome. In the female about 20 per cent or more of the cells in a buccal smear show a chromatin mass adjacent to the nuclear membrane – the so-called sex chromatin named, after its discoverer, the Barr body. None of the cells of a normal male shows this Barr body. The weight of present evidence indicates that the Barr body represents the heterochromatin portion of one x chromosome and is formed by a process which is termed "fixed determination" and is presumed to be genetically inactive. Mary Lyon was among the first to propose that only one x chromosome is genetically active during the cell-division interphase; the other x chromosome in the normal female retains its heterochromatic properties (i.e., inactivity). In early embryogenesis each somatic cell of the female reaches a "time of decision" as to whether x^p or x^m shall be the active x chromosome in that particular cell. Descendants of each cell abide by the decision originally made. Thus such decisions are made randomly.

When Dr. McCulloch and his father originally presented this family at

the Academy, I had the honor of discussing. In that discussion I proposed the term, sex-linked intermediate inheritance by which to explain the "intermediate" state of expressivity in the retina of carrier females. According to Mary Lyon's hypothesis, approximately half of her active x chromosomes would be bearing the mutant gene for choroideremia. Thus two populations of cells could exist, those with the normal x chromosome being active and those with the x chromosome bearing the mutant gene for choroideremia being active. Thus, one could anticipate that in the moth-eaten area of the female retina the clone of cells originated from the cell bearing the activated mutant–gene–bearing chromosome and in the normal retina areas the cells originated from the cell bearing the normal x chromosome.

Since the selection of the x chromosome is random, it is entirely possible to conceive that large proportions of the retina could either be normal or have "choroideremia" and thus explain the considerable variability in expressivity exhibited by "choroideremia-carrying females." Some females are severely affected; others very minimally. This is true in choroideremia females and also in another variety of sex-linked intermediate inheritance – albinism of the eye alone.

Besides the Mary Lyon's hypothesis, I want to discuss the idea of mythology, or, shall I say, a "curse" on the family.

Just about 90 miles to the north of us, in West Virginia, lives a large family of coal miners of Welsh extraction exhibiting epidermolysis bullosa, a skin disease presenting bullae of the skin and, when severe, bullae of mucous membranes affecting the eye.

This family has an interesting folklore to the effect that many centuries ago members of their family were amiss in paying their taxes. Several of them were hanged as "examples" to the living delinquent members. In retribution, one of the tax collectors was hanged, but before he died he "put a curse on us." The tax collector's skin had been stripped from a large portion of his body by his executors and this family now believes that their skin blisters are the consequence of that "curse" of past centuries ago. When I pointed out to the family that the disease only affected 50 per cent of them, it seemed to make no difference, since they believe that all members of the family carry the "curse."

Another example of a family curse is a family in which primary amyloidosis is rampant. This family, of Swiss descent, is convinced that "the Dubachs die early" since a curse was placed on their family in the early seventeenth century – again a direct result of trouble with the local constabulary. Since most affected individuals die of myocardial insufficiency, I would agree that "the Dubachs die early."

Finally, I should like to mention that awareness of the "typical carrier female retinal change" will be a value to you both diagnostically and prophylactically. By recognizing the carrier female picture you can more easily diagnose the early retinal changes in young affected males and can also tell such "affected" women that they can transmit the severe disease to 50

per cent of their male offspring and the mild state to 50 per cent of their female offspring.

DR. A. EDWARD MAUMENEE. I would like to add my congratulations to Dr. McCulloch on his Herculean study of the genetics of choroideremia.

As far as the fluorescein angiography is concerned in these cases, the patent larger choroidal vessels fill very rapidly so that if the pictures are not taken immediately after injection of the contrast medium, the fluorescence might be missed. We have done fluorescein angiography on two patients with choroideremia who had small central islands of normal tissue but field defects to 20° of fixation. Their larger vessels filled with fluorescein.

When the choriocapillaris remains in the macular area it can be seen on angiography. Fluorescein does leak or diffuse from these capillaries into the more involved atrophic surrounding area. I think Dr. Cogan also had a very nice example of fluorescein angiography on such a patient who showed the same findings.

I might add that in some patients with retinitis pigmentosa there is also an absence or defect in the choriocapillaris on fluorescein angiography and on histology.

DR. ARTHUR LINKSZ. May I say that I am so delighted with this beautiful paper that I just have to say a few words.

All during the reading I was wondering whether the author did or did not do any color-vision tests. He did, but I guess the test he chose is not the right type of color-vision test for people with poor vision. It would be better if in the future the author would use either the H-R-R Test (which reveals not only red and green, but also yellow and blue defects) or preferably the Farnsworth D-15 Test, which can give results even if visual activity is poor. It gives at least as much information as the very elaborate and complicated Farnsworth 100-Hue Test.

May I mention that a few years ago I published a paper in the American Journal of Ophthalmology on the D-15 test. With my usual modesty, may I say that it is a very informative paper. People who want to test color vision in cases of ocular pathology should, I think, read it.

DR. CLEMENT MCCULLOCH. I would like to thank the discussers very much.

Firstly, replying to Dr. Linksz, we did the Hardy-Rand-Rittler test, the Ishihara test, and the Farnsworth 100-hue test on a great many of these patients. We could not test all of them, because some of them were examined in barns, in the field, and in log cabins.

Concerning the clone theory. I would like to thank Dr. Falls. Certainly, when one looks at the female fundus, one appears to be looking at clones of normal and affected cells, and it certainly is a very impressive appearance, thinking of that theory.

Concerning the vessels that Dr. Wise mentioned, the material would seem to confirm Dr. Wise's remarks.

The second pathologic case of a 43-year-old man is to the point. There was other pathology in the eye, but I will deal only with the retinal pathology. In the midperiphery there is a bit of choroid and a bit of degenerate retina there in the top. This eye has the earliest retinal changes we so far have obtained. There are little tufts of cones opposite withered choroid and pigment epithelium. At high power, one can see the pigment epithelium, the cones, and their nuclei. The outer part of the visual receptive elements is missing, as if the cones had shrivelled from the outside in. The appearance would make one think that the disease is affecting the cones from the pigment epithelium inward.

In other words, the retina farther in is better, but death is occurring next to the pigment epithelium.

Dr. Wise's thought that the oxygen tension is indeed lower in these cases and, therefore, there is not stimulation for secondary changes in the retinal vessels may, indeed, be confirmed by this pathology.