RETINOSCHISIS—RETINAL CYSTS

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IT IS THE PURPOSE of this paper to present material illustrating various aspects of the heredity, the clinical manifestations, the pathology, and the therapy of retinoschisis and retinal cysts. Retinoschisis is defined as a splitting of the neural layers of the retina. If this condition presents itself in form of a circumscribed bullous elevation, the term retinal cyst seems to be more appropriate. However, in the literature both terms are often used interchangeably. It is emphasized that in this study retinoschisis is identified as both a clinical and pathological disease entity.

CLASSIFICATION AND CLINICAL CHARACTERISTICS

This is based on the author's personal observations, Ricci's work,[64] and suggestions made by Falls.[65] The various forms of retinoschisis are classified as follows:

A. HEREDITARY RETINOSCHISIS

1. Gonosomal (sex-linked) juvenile retinoschisis
2. Autosomal juvenile retinoschisis
3. Bilateral juvenile peripheral giant cysts
4. Presenile and senile retinoschisis
5. Goldmann and Favre's "idiopathic retinoschisis with premature hemeralopia"
6. Microcystic chorioretinal and hyaloideal abiotrophies

B. ACQUIRED OR ENVIRONMENTAL RETINOSCHISIS AND GIANT CYSTS

In this presentation our main attention will be concentrated on the macrocystic forms of retinal splitting to which the terms "retinoschisis" and "giant cysts" are commonly applied.

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A. HEREDITARY RETINOSCHISIS

1. Gonosomal (Sex-linked) Juvenile Retinoschisis

As a rule, this disease entity is observed in males with a recessive sex-linked hereditary trait. It is interesting that the first such cases, including two of my own, were published under a variety of names[1–5,7–25] which did not precisely reflect the true nature of the disease despite Wilczek's[6] publication in 1935 in which he used the term "retinoschisis" in the title of his paper. The clinical pathology of "retinal splitting" has been described previously by Bartels[4] in 1933. Both of his cases were associated with retinal detachment. Samuels and Fuchs[19] employed the term "retinoschisis" in their textbook, published in 1952. In 1953, Jager[21] reported on six families with twenty-five male siblings afflicted by "retinoschisis." Since then this term has come into general use.

Many ophthalmologists still employ the term "congenital vascular veils in the vitreous" synonymously with the term "juvenile retinoschisis." The former term was introduced by Ida Mann and MacRae[8] in 1938. However, from the description given by Ida Mann in her book, *Developmental Abnormalities of the Eye,* published in 1958, and from the case described in 1960 by Goodside,[27] one gains the impression that "congenital vascular veils in the vitreous" represent a distinct disease entity. The nature of this veil-like structure is a vitreous condensation which at its start is in contact with the inner layer of the optic cup, whereas in retinoschisis the cleavage lies within the neuroepithelial layer itself. Hence, the former shows an irregular vessel pattern in the vascularized preretinal tissue, whereas the latter displays the original though slightly altered, retinal vessel pattern in the inner layer of the split retina. Occasionally, the retinal vasculature is so divided that some of the vessels also run in the outer layer of the retinoschisis. Only in very rare instances are there freely suspended retinal blood vessels in the vitreous. The most significant difference between these two conditions is that the "congenital veils in the vitreous" are present at birth, whereas retinoschisis develops later.

The following concordant clinical characteristics were found in the four eyes of 13-year-old monozygotic twins reported by the author[10] in 1940: (1) projection of the translucent membrane-like inner layer of the split retina into the vitreous carrying with it the retinal vasculature in the lower temporal quadrants (Figure 1); (2) large oval and smaller round or horseshoe-shaped holes of the inner layer of the retinal schisis; (3) intraretinal grayish opalescence with absence of

retinal edema suggesting reactive gliosis within the remaining neural tissue of the inner and outer walls of the retinal cleavage; (4) characteristic degeneration of the macula (Figure 2); (5) typical lattice degeneration of the retina between equator and ora serrata on both sides of the cystic areas; (6) chorioretinal atrophy and granular pigment changes slightly aside and posterior to the areas of retinal splitting as depicted in Figure 2; (7) partial optic atrophy; (8) relative central scotoma and peripheral suppression of the visual fields corresponding to the areas of schisis; (9) hyperopia and astigmatism; (10) lack of noticeable vitreous pathology in the eyes not complicated by retinal detachment.

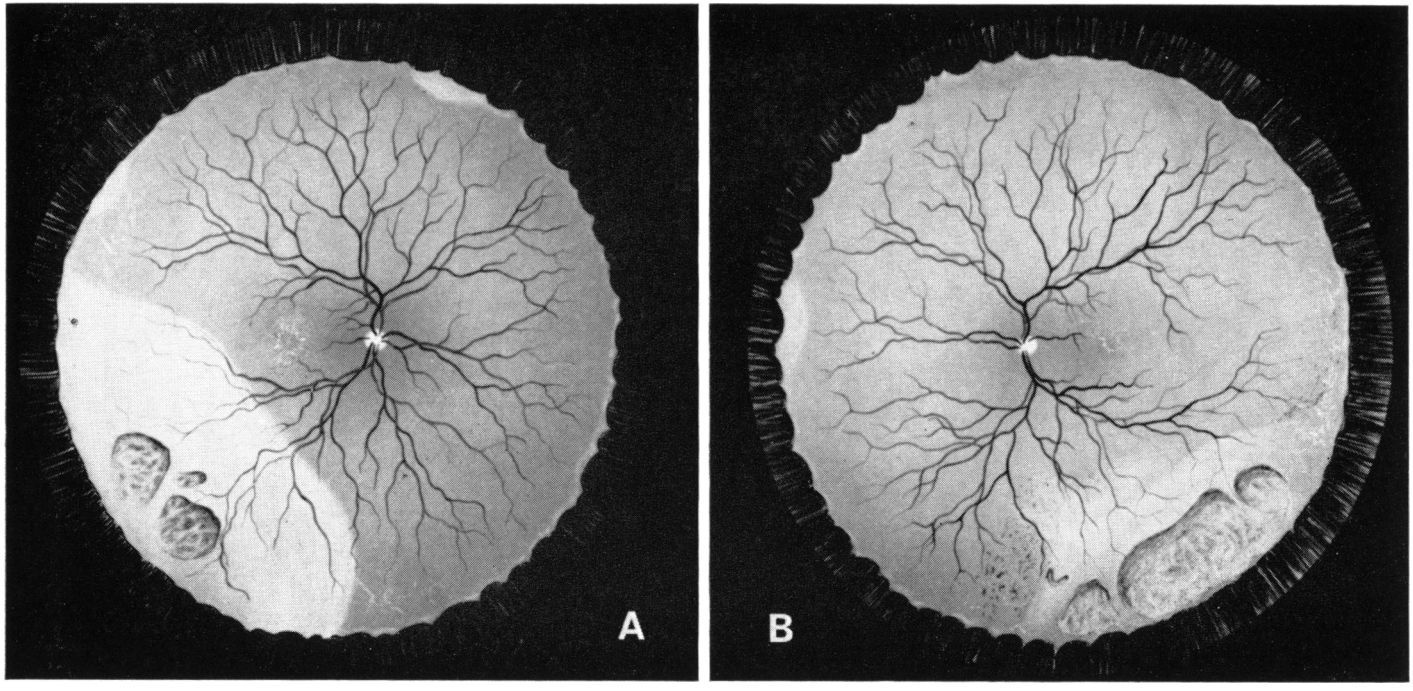
Discordant findings were true retinal detachment and preretinal fibrous tissue organization extending over almost the entire fundus of the left eye of one of the twins (Figure 1D). Since the appearance of the fundi remained virtually stationary over a period of more than five years, I did not operate.

The fixed position of the retina in the area of splitting can be attributed to the fact that the vitreous overlying the retinoschisis was neither detached nor liquefied and that the content of the cavity of the schisis seemed to be very tenacious. Similar clinical observations were made by Lindner[5] and Rieger.[11]

In 1963, the author had the opportunity to study a family with recessive X-chromosome–linked retinoschisis involving six generations (Figure 3). Fourteen members of this kinship, ranging in age from 4 to 63 years, gave a history of "retinal detachment" and "macular degeneration." Ten of them were examined by the author. All ten displayed distinct features pathognomonic of retinoschisis, although with varying degrees of expressivity, as illustrated in Figure 4. The appearance of the partially atrophic disk with perivascular sheathing and the characteristic configuration of the macular lesion found in the propositus* are depicted in Figure 5A. The well-known, although unspecific, phenomenon of shadow casting of the retinal blood vessels was noticeable in the eyes with transparent inner walls (Figure 5B) but was absent in those cases in which gliotic opalescence of the inner layer of the retina was present (Figure 5C).

Photocoagulation produced white effects in the outer layer of the schisis but the inner layer essentially unaffected (Figure 5D). Other concordant findings were hyperopia and arborization of the peripheral retinal vasculature partially replaced by superficial white

*I am indebted to Doctor William Middleton of Alton, Illinois, for the referral of this patient.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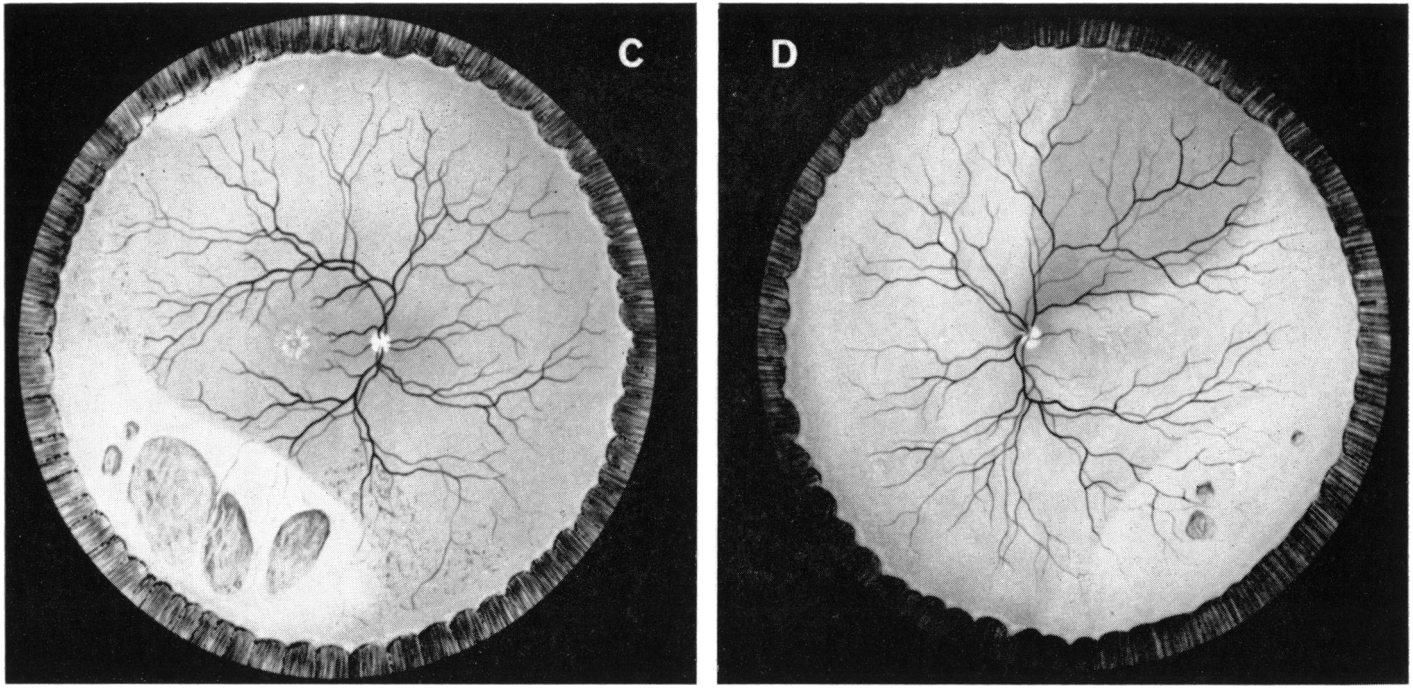


FIGURE 1. FUNDUS DRAWINGS OF MONOZYGOTIC TWINS WITH GONOSOMAL RECESSIVE JUVENILE RETINOSCHISIS IN INFERIOR TEMPORAL QUADRANTS.

Concordant findings in A, B, and C; discordant findings (posterior vitreous and retinal detachments) in D. For further explanations see text.

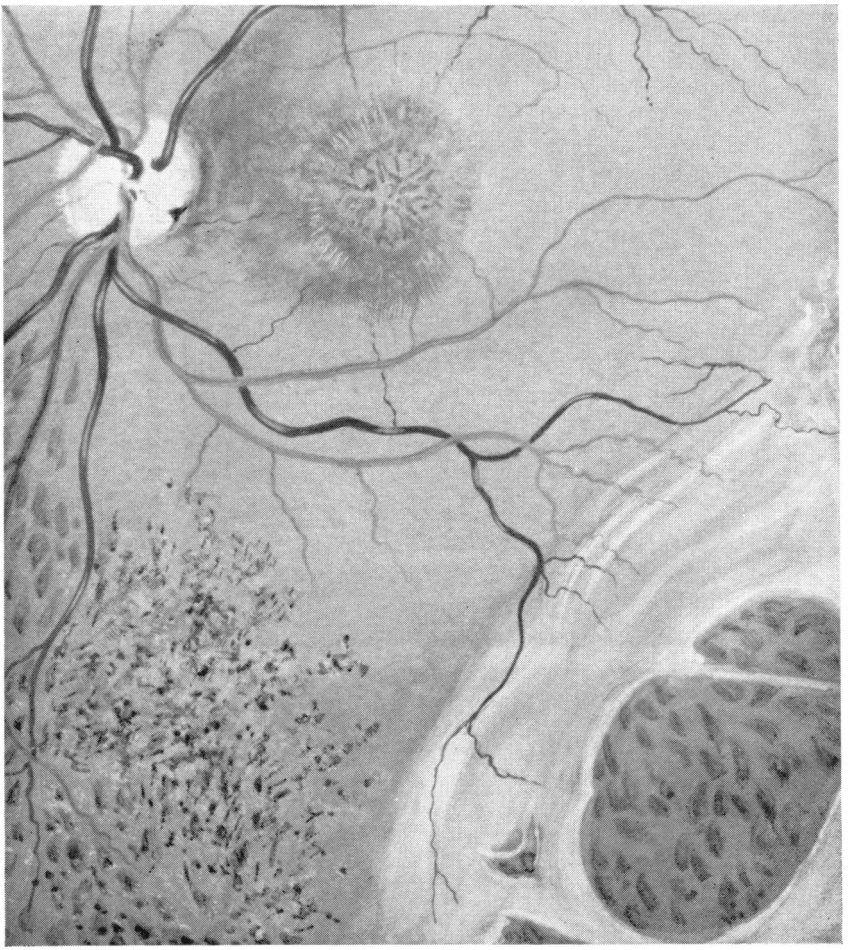


FIGURE 2. SAME AS FIGURE 1B.

Fundus drawing made by the author showing optic atrophy, macular degeneration with star-shaped deposit of yellowish pigment and retinoschisis in the lower temporal quadrant.

lattice-like markings of the retinal tissue as described by Balian and Falls.[26]

Discordant findings were: (1) vitreoretinal hemorrhages in the youngest affected member with sheathing and partial obliteration of the terminal vessels similar to the vascular changes described by Meyer-Schwickerath[36] in cases of Eales's disease; (2) spontaneous retinal detachment in one eye of three patients (Nos. 2, 5, and 8, in

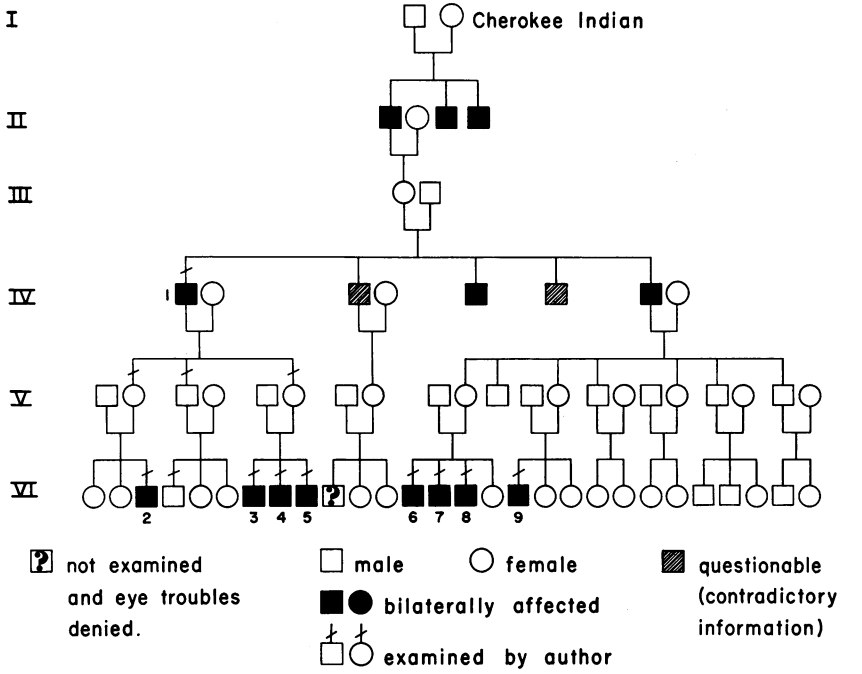


FIGURE 3. PEDIGREE OF FAMILIAL RETINOSCHISIS AND MACULA DEGENERATION WITH SEX-LINKED RECESSIVE TRANSMISSION OF INHERITANCE.

Figure 4); (3) spontaneous pigmentary demarcation of the schisis in one eye of the patient # 4; (4) amaurosis and calcified complicated cataract in the right eye of patient # 5; (5) "dendritic" and filariaform degenerations in the inner layer of the schisic retina in both eyes of patient # 6 (Figure 4). Figure 5C illustrates these "dendritic markings" observed in the temporal area of the fundus. Thomson,[3] in 1932, described similar markings located near the disk in the eyes of one of four affected brothers. Similar observations were later reported by Levy[17] (1952), and by Balian and Falls[26] (1960).

In the affected cases of this family the vitreous appeared condensed and firmly adherent to the area of retinal splitting except when these changes were complicated by retinal detachment. In the latter condition, liquefaction of the vitreous and detachment of the posterior hyaloid membrane were invariably present.

Chromosomal studies attempted in two members of this sibship were unsuccessful.* Cytogenetic studies performed in other cases of sex-

*For unexplained reasons repeated blood cultures failed to grow.

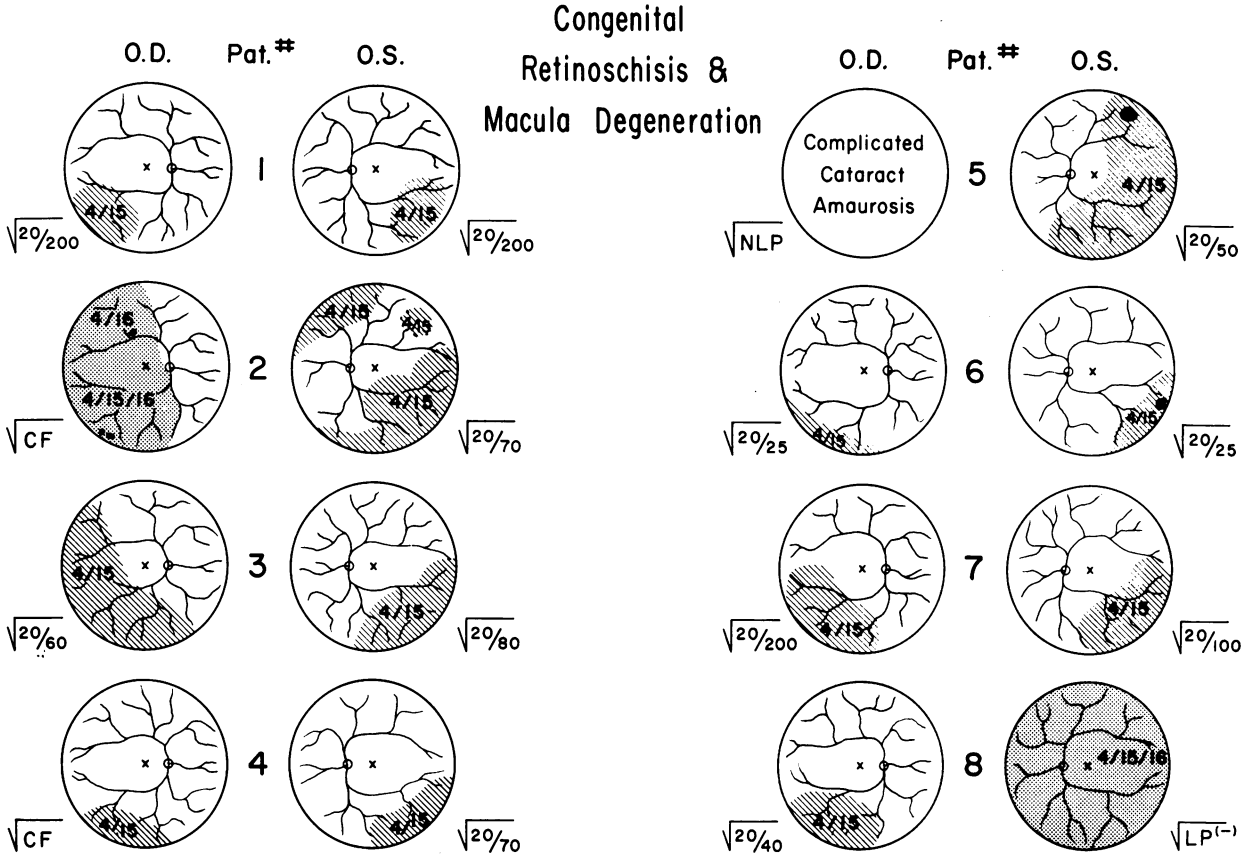


FIGURE 4. FUNDUS SKETCHES OF THE SIBLINGS 1 TO 8 IN FIGURE 3 ILLUSTRATING DISTRIBUTION OF RETINOSCHISIS (HATCHED). Notice retinal detachment (dotted) in patients 2 and 8. Black spots indicate holes of the inner wall of the schisis. #4=formed secondary vitreous with normal vitreo-retinal border structure, #14=hyaloid membrane detached ("vitreous detachment"), #15=retinoschisis. #16=retinal detachment.

linked retinoschisis with recessive mode of transmission of inheritance (Figure 6) proved to be normal.

The clinical picture of the recessive sex-linked form of retinoschisis varies not only within the same kinship but even more so among affected members of different sibships. The most consistent change is the maculopathy which in all four affected siblings of Figure 6 resembled the picture shown in Figure 5A. In two cases it has been observed at the age of 1 and 1½ years, before any signs of retinoschisis and before a slight degree of "whitish mottling" of the pigment epithelium in the lower temporal quadrants of the eye could be discovered.

In 1963 the author treated two boys under the age of 5 years, sons of two sisters belonging to another family with an established gonosomal recessive trait of retinoschisis. In both patients the retinal splitting developed into total retinal detachment. In each case the vitreous of both eyes was completely liquefied. Histopathologic examination of an aspiration biopsy sample taken from the vitreous during surgery revealed fragments of condensed collagenous tissue with evidence of hemosiderosis. The appearance of the blood vessels in this case again was compatible with that of Eales's disease with perivascular sclerosis and partial or total obliteration of the peripheral branches of the retinal vessels.

In another case of juvenile retinoschisis involving a 2-year-old boy, we found extensive retinal splitting in both eyes with large "kissing" bullas of the retina meeting each other in the horizontal plane. The retinal vessels in this case were present in both the inner and the outer wall of the schisis in the right eye, but only in the inner wall of the left eye. Photocoagulation of the entire area of cleavage effected the complete collapse of the schisis within the surprisingly short period of nine days. The macular area was not grossly affected but was covered by the bullous elevations of the retina prior to the photocoagulation treatment. The 6-year-old brother of this patient had a moderate retinoschisis in the lower temporal quadrant of both eyes without formation of retinal holes and associated with an apparently normal vitreous. Neither parent revealed any indication of ocular pathology.

2. Autosomal Juvenile Retinoschisis

This form of hereditary disorder is extremely rare. It is easily distinguished from the recessive sex-linked form since it occurs in families in which females are affected. Fitzgerald and McCarthy[29] reported

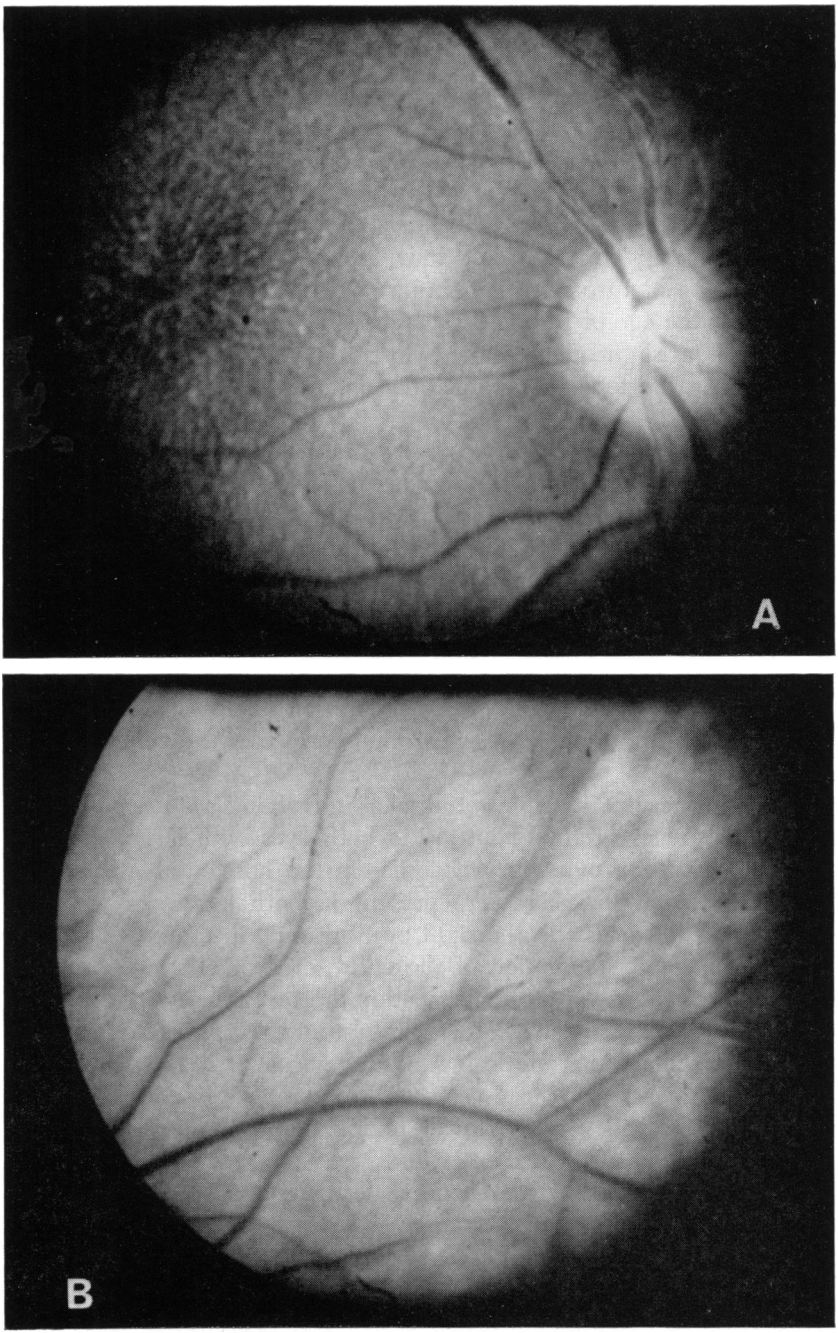
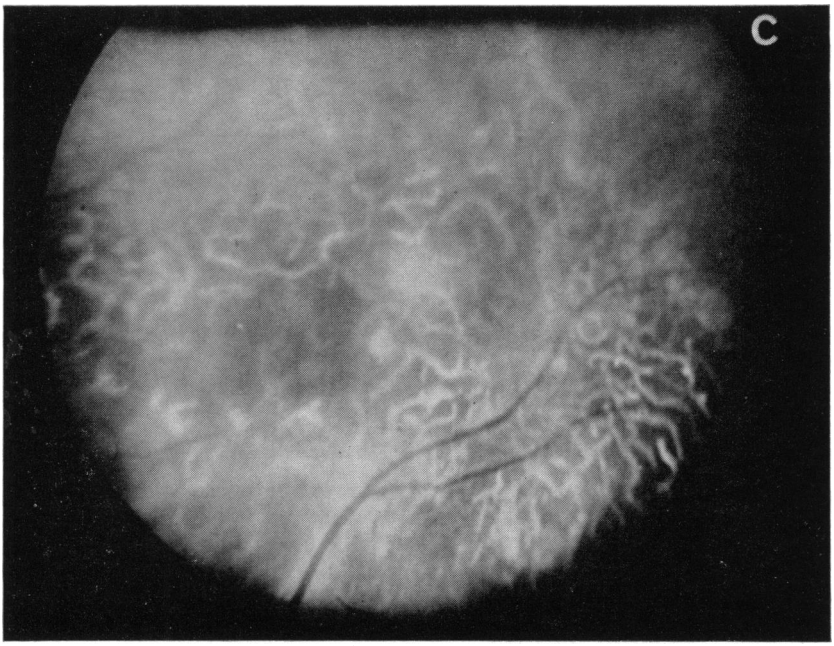
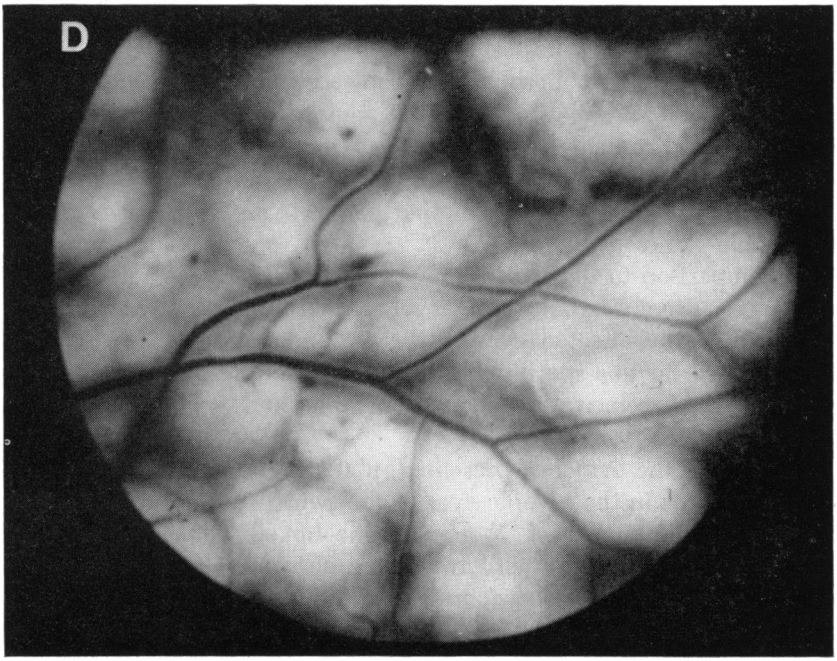


FIGURE 5. FUNDUS PHOTOGRAMS TAKEN FROM SIBLINGS BELONGING TO PEDIGREE IN FIGURE 3.

A, Macula degeneration with yellowish granular material in tapetum radially arranged. Similar lesions were found in the eyes of the identical twins related to Figure 1. Notice partial optic atrophy and sheathing of the blood vessels. B, Shadow casting of retinal vessels over area of retinal splitting.





C, "Dendritic markings" or filariaform degeneration in the area of retinal splitting. D, Same as B after photocoagulation. Notice that inner wall of schisis is not affected.

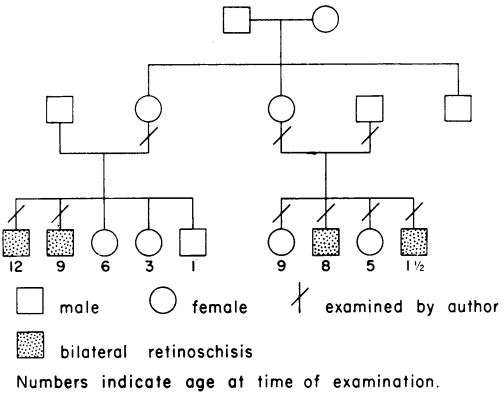


FIGURE 6. PEDIGREE OF FAMILY WITH BILATERAL RECESSIVE SEX-LINKED TRANSMISSION OF RETINOSCHISIS.

two cases of retinoschisis occurring in a mother and her son, possibly indicating dominant inheritance. Figure 7 demonstrates schematically the distribution of the retinoschisis found in the myopic eyes of a pair of female monozygotic twins, who were 19 years old when they were examined for the first time by the author. The pertinent pedigree is shown in Figure 8. The retinal pathology was relatively advanced and associated with a posterior vitreous detachment in either eye. It was of interest that both sisters showed peripheral blood vessel anomalies again compatible with the angiopathy observed in Eales's disease, and that their grandmother had recently developed a retinal detachment which originated in an area of retinoschisis. The fundus examination of the hyperopic mother of the twins did not reveal any noticeable pathology.

In comparison to the typical picture of macular degeneration found in the recessive sex-linked cases of retinoschisis, the maculopathy observed in the affected eyes of this group of retinoschisis patients appeared to be non-specific, consisting of chorioretinal atrophy and pigment displacement as seen in myopic and senile abiotrophic maculopathies.

In view of the evidence presented, it seems unlikely that the cases of retinoschisis in the myopic eyes of the twin sisters represent homozygotic manifestations of X-chromosome–linked defect. It is more likely that one is dealing with an *autosomal form of retinoschisis with recessive or, possibly, even dominant transmission of inheritance.* The cytogenetic study of cultured white blood cells revealed a normal

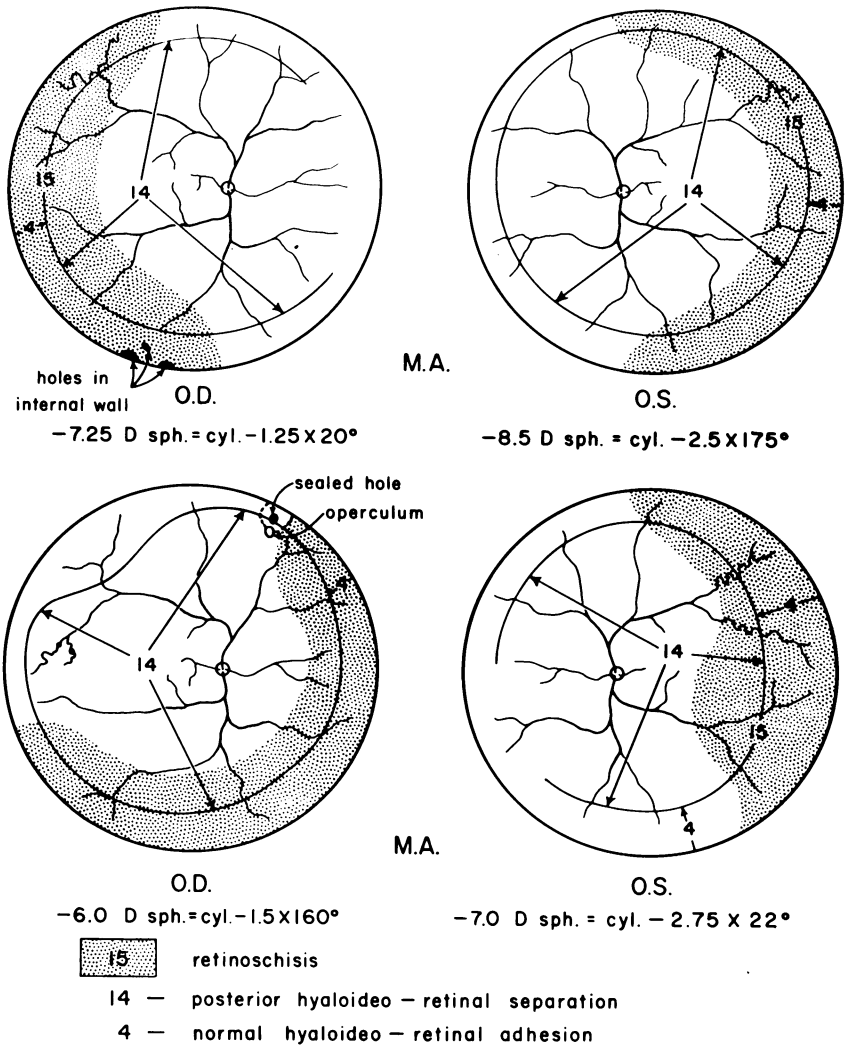


FIGURE 7. FEMALE TWINS WITH BILATERAL SCHISIS (DOTTED, ZONE #15) DIAGNOSED AT AGE OF 19.

modal number and structure of the chromosomes in both of these patients.

3. Bilateral Juvenile Peripheral Giant Cysts

Both forms of retinoschisis previously discussed differ from the peripheral (postoral) giant cysts which predominantly develop in the

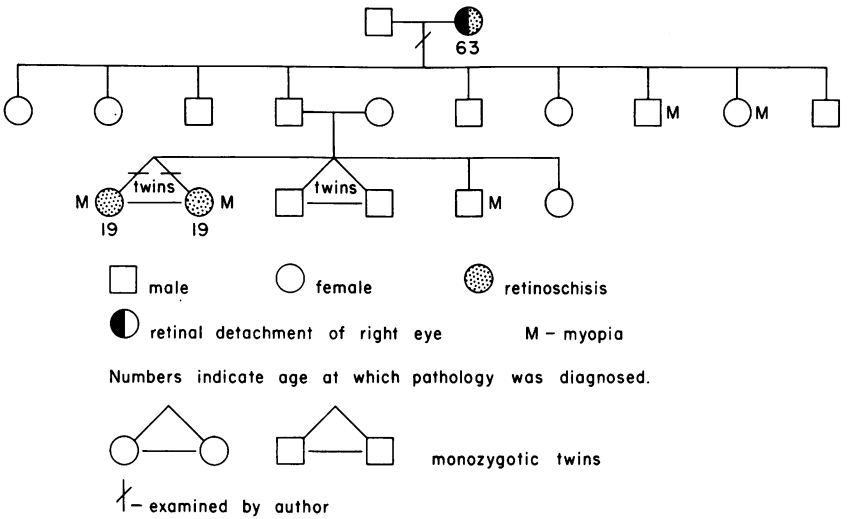


FIGURE 8. PEDIGREE OF FAMILY RELATED TO THE FEMALE TWINS OF FIGURE 7.

lower temporal quadrants of the eyes of either sex. The fact that most of those patients afflicted by this condition are juveniles and that more than 50 per cent of our patients revealed such lesions in mirror symmetry suggests that one is dealing with a developmental anomaly on either a genetic or acquired basis. Autosomal recessive transmission of inheritance, or mutations, or phenocopies are possibilities to be considered.

In four of our patients large peripheral cysts caused an epithelio-retinal separation without breaks (Figure 9A). Weve[37] very appropriately called this type of retinal detachment "décollement par soulèvement," i.e. retinal detachment by elevation through forces acting from below. Retinal breaks frequently develop either by overstretching of tissue between the ora and the cyst (Figure 9B), or by disintegration of the inner and outer walls of the cavity of the cyst. Similar findings were reported by Csillag.[38,59] In our material were three cases of retinal detachment produced by juxta-oral breaks in connection with large oral cysts. A detailed study of the pathogenesis of the *Cysten Ablatio* has been published by Hruby[39,40] in 1956 and in 1964.

The combination of retinal detachment with solitary or multilocular giant cysts is not infrequently encountered in long-standing idiopathic retinal detachment (Figure 10). In the last eight years, twelve such patients, ranging in age from 7–25 years, were observed in our clinic.

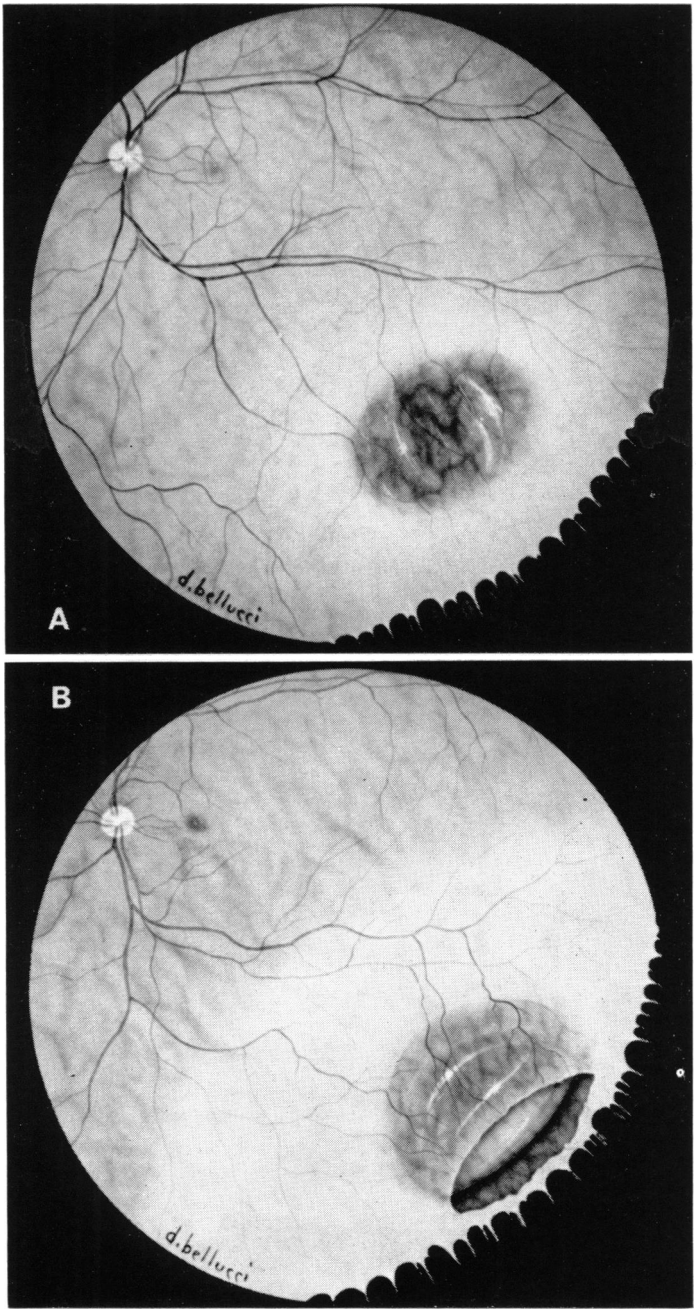


FIGURE 9

A, giant cyst in inferior temporal quadrant with retinal detachment around the cyst (*décollement par soulèvement*, Weve[37]). B, retinal detachment with break (*par soulèvement*). Notice outer wall of cyst visible through the break.

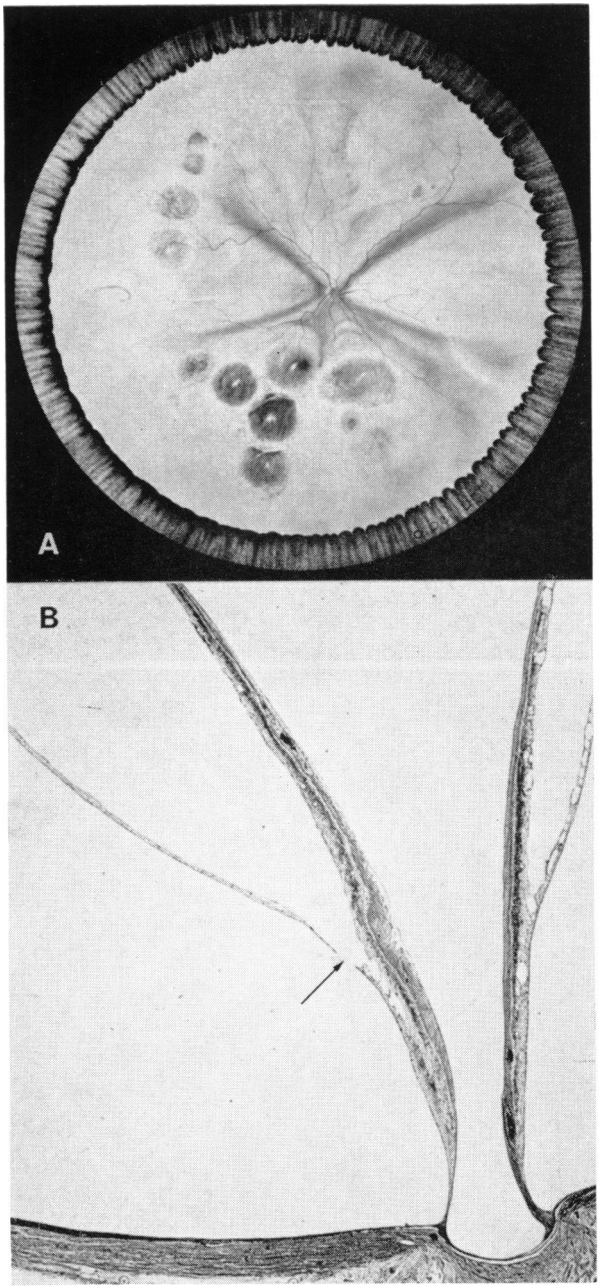


FIGURE 10. MULTIPLE GIANT CYSTS OF RETINA.

A, fundus picture of unilateral retinal detachment with multilocular giant cysts associated with open-angle glaucoma in a 14-year-old boy. B, histological picture of a case of retinal detachment with giant cysts. Notice break in the outer wall (arrow) and glaucomatous excavation of optic disk.

Seven of them presented with the combination of unilateral retinal detachment with giant cysts and open-angle glaucoma, the remaining five without glaucoma.

The combination of young age, multilocular retinal giant cysts, unilateral open-angle glaucoma, and unilateral detachment of the retina suggests that one is dealing with an environmental syndromal disorder of unknown etiology. However, just recently I have learned from Robert Shaffer[41] that this symptom complex has been observed bilaterally in several instances. This, of course, indicates that heredity cannot completely be ruled out.

4. Presenile and Senile Retinoschisis

There is evidence of familial occurrence in presenile and senile retinoschisis. Both conditions are more prevalent than the juvenile form. They also tend to occur bilaterally and in mirror symmetry. Not too long ago, I observed retinoschisis in three elderly sisters of one family (Figure 11). All three were emmetropic or slightly hyperopic and exhibited a relatively flat but extensive retinal splitting in the

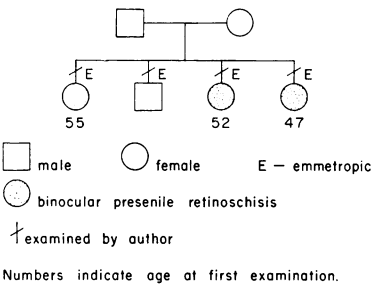


FIGURE 11. PEDIGREE OF A FAMILY WITH PRESENILE BILATERAL RETINOSCHISIS.

upper temporal quadrant of each eye, whereas a brother did not reveal any pathology of the fundus. In one of these patients the schisis had reached the macula in one eye and approached the corresponding area in the other. Photocoagulation applied over the entire region of recognizable retinal splitting effected a collapse of the schisis with the formation of a chorioretinal scar. Even though photocoagulation effects were placed extremely near to the macula, the retained vision is 20/20, and there is no metamorphopsia.

The mirror symmetry of the retinal pathology in these three siblings speaks for a genetic background with evident control of location,

extension, time of commencement, and rate of progression of the pathology involved. However, since we do not know anything about their antecedents it is perhaps presumptuous to suggest that one is dealing with a recessive mode of transmission of inheritance.

As far as the clinical picture is concerned, senile and presenile retinoschisis present similar fundus changes. In the early stages, one finds an exaggeration of the peripheral cystoid degenerations which respond to scleral indentation by losing some of the transparency of the inner layer, a phenomenon which is commonly referred to by the expression "white with pressure." However, in an equal number of instances the retinal surface in the area of beginning schisis appears "white without pressure" due to the condensation of the vitreoretinal border structures and to the formation of dense foot plates of collagenous fibers which firmly adhere to the surface of the inner wall of the schisic area and extend into the vitreous. As a rule, these fibrous elements are perpendicularly oriented to the retina. The foot plates can give a silk-like glistening effect without and with scleral indentation, similar to the *état givré* of Gonin.[42]

In more advanced stages the outer layer of the schisic area may assume a faint gray haze of diffuse or irregular distribution as depicted in Figure 12A. Round pits or oval holes may form in the outer wall (Figure 12B). Microcystic changes in the macula may accompany the peripheral changes. Only in a few exceptions have large macular cysts been observed (Figure 13A). In general, the condition progresses at a very slow rate and may become temporarily arrested. In a few cases one finds demarcation lines formed either by gliotic proliferation as shown in Figure 14A or by a more or less pigmented chorioretinal scar as depicted in figures 14B and 14C. Pigmented highwater marks have been described by Sorsby.[24] In this way progression may be arrested in the direction of the posterior pole. However, the schisis generally extends circumferentially until it eventually encompasses the entire periphery of the fundus. Breakthroughs of the demarcation lines have been observed. In far advanced stages the schisic elevation can reach excessive degrees and large bullous elevations may form (Figure 15). The inner wall of this large elevation can be crystal clear or may present itself with a gray haze similar to the appearance of watered silk. Blood vessel pathology resembling the perivascular changes in lattice degeneration (Figures 12B and 15) or Eales's disease invariably accompanies the schisic changes.

As far as the vitreoretinal relation is concerned, the findings vary within a wide range. Usually one finds vitreoretinal adhesions over the area of retinal splitting (Figure 16C). Shea, Schepens, and Pirquet[43]

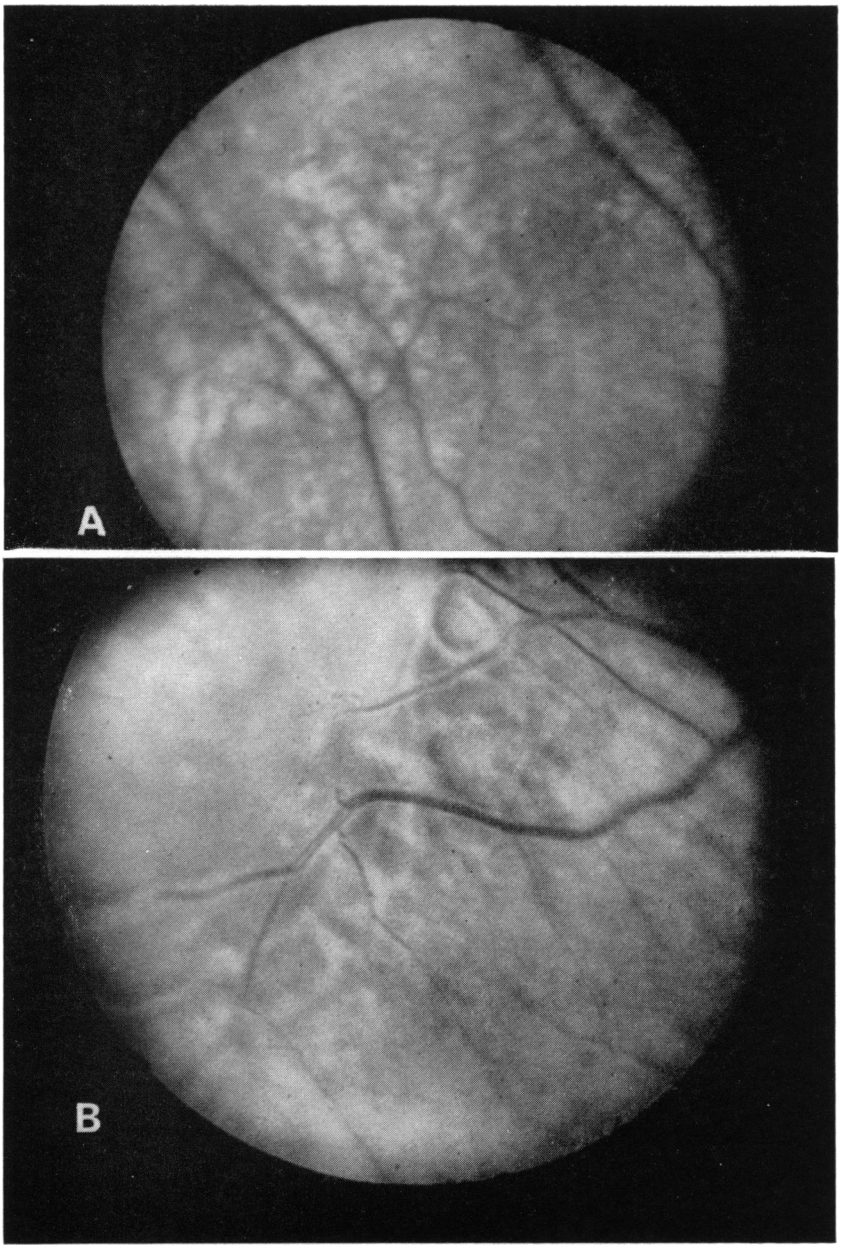


FIGURE 12

A, mottling of the outer wall in a case of senile retinoschisis. B, pitting and beginning of the formation of holes in the outer wall in a case of senile retinoschisis. Notice angiopathy in area of schisis.

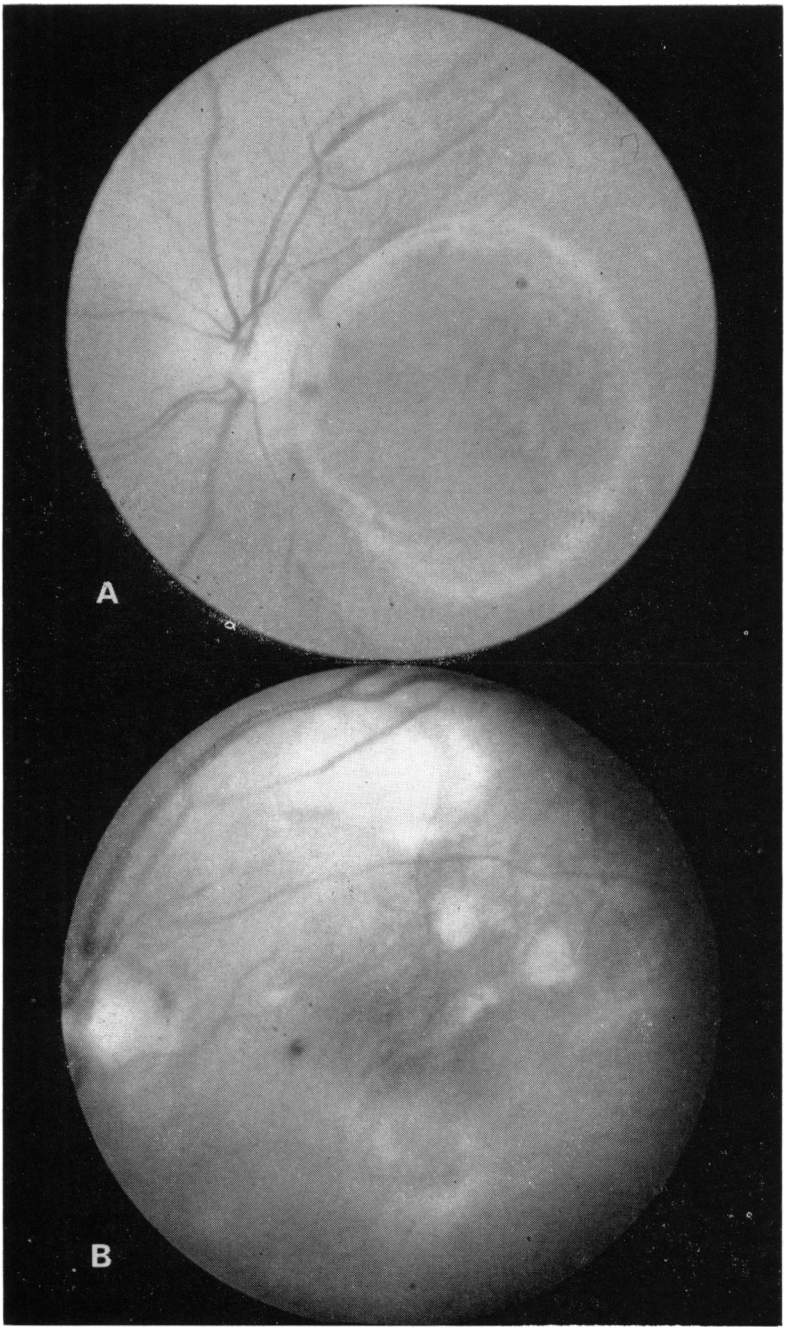


FIGURE 13. GIANT MACULAR CYST IN EYE WITH RETINAL DETACHMENT.
A, before retinal detachment surgery; B, three days after peripheral surgery of the retina and photocoagulation of the temporal half of the macular cyst.

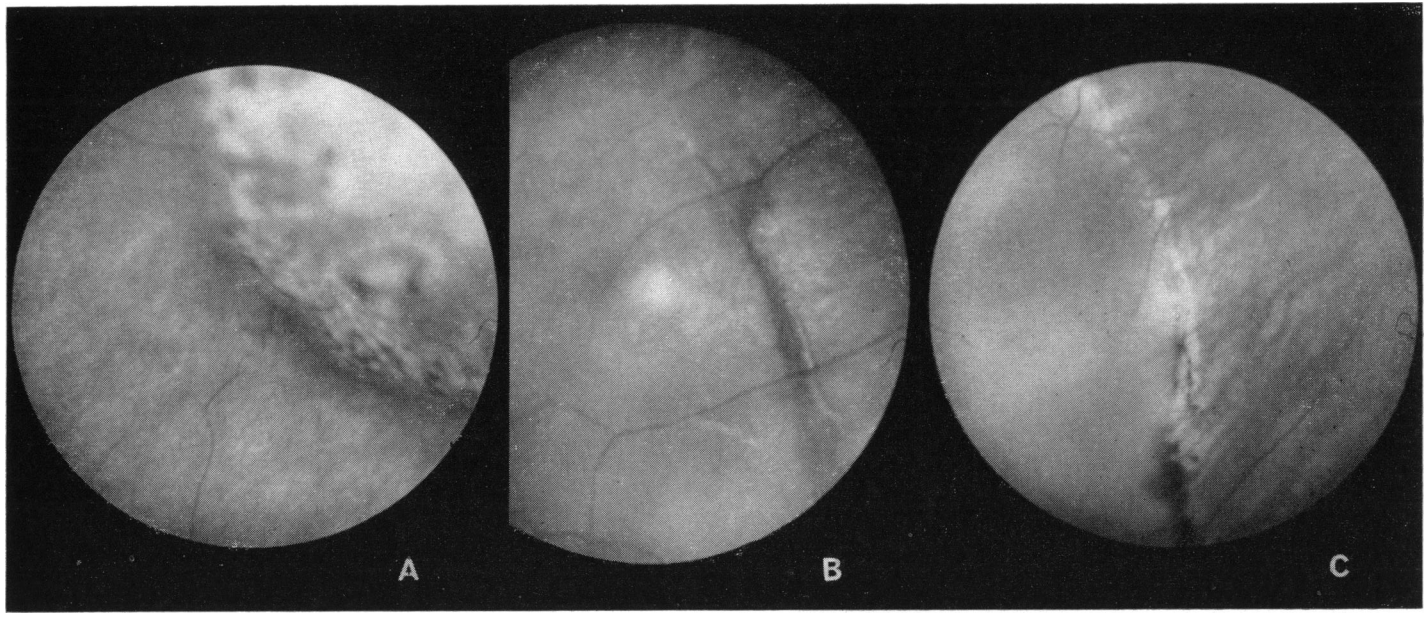


FIGURE 14. EXAMPLES OF SENILE RETINOSCHISIS WITH DEMARCATION LINES.

A, elevated and pitted demarcation zone; B, pigmented ridge of demarcation; C, atrophic and slightly pigmented demarcation zone.

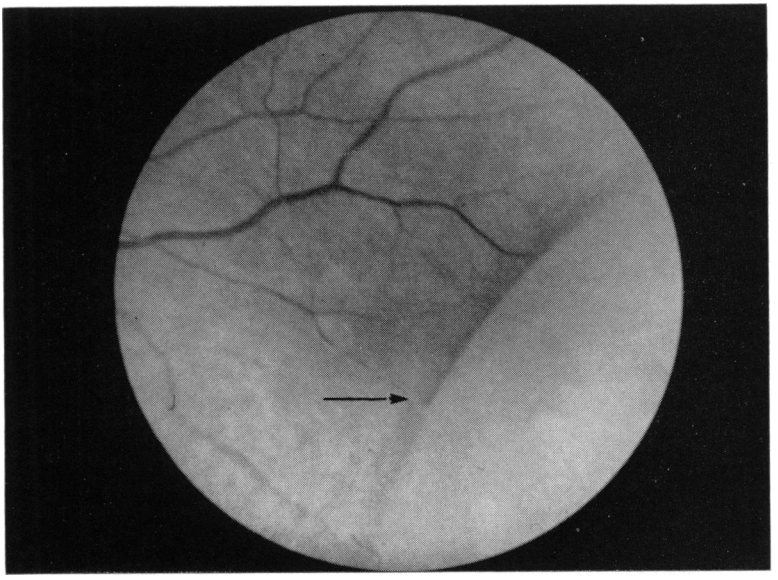


FIGURE 15
Bullous retinoschisis (giant retinal cyst) with sclerotic retinal vessel (arrow) in vicinity of the split retina.

reported posterior vitreous detachment in 41 out of 58 retinoschisis patients examined for that purpose. However, whenever they were able to establish the hyaloideoretinal relation, the vitreous seemed to adhere to the retina over the area of splitting. Our findings, in principle, agree with theirs but differ in so far as at least 20 per cent of all cases, including the juvenile form of retinoschisis, revealed evidence of hyaloideoretinal separation involving either parts or the entire area of retinal cleavage (Figure 16D).

5. Goldmann's and Favre's Idiopathic Retinoschisis with Premature Hemeralopia

A synonymous term for this ocular disease entity is "hyaloideotapetoretinal degeneration." The cases reported by Goldmann and Favre[44] in 1958 consist of a brother and sister with peripheral retinoschisis, peripheral chorio-tapetoretinal pigment changes, and profound vitreous alterations. The macula showed changes similar to microcystic edema which by biomicroscopic examination turned out to be preretinal fibroplastic tissue. These 16- and 17-year-old patients were re-examined by Ricci[45] who found, in addition, annular scotomata and hemeralopia associated with abolishment of the ERG.

6. Microcystic Chorioretinal and Hyaloideal Abiotrophies

This group comprises: (*a*) the senescent peripheral cysts (Blessig's cysts, Iwanoff's "edema")[46–57]; (*b*) the simple circumferential abiotrophies or "snail tracks" (*état givré* of Gonin[42]), if they are associated with cystic changes; (*c*) the "cystoid degenerations" of Gonin[42] and Vogt[69]; (*d*) the various forms of Vogt-Gonin's *Gitterlinien* or "lattice" degeneration (Schepens[66]) which are commonly but not necessarily associated with microcystic changes; and (*e*) macular cysts in connection with familial tapetoretinal macular degeneration.

All representatives of this group predispose to retinal hole formation. They are often referred to as "rhegmatogenic" chorioretinal and hyaloideal degenerations. The microcystic changes pertinent to types *a* to *e* are often found in assiciation with retinoschisis.

B. ACQUIRED OR ENVIRONMENTAL RETINOSCHISIS

The most common form of this category of retinoschisis is the one associated with long-standing idiopathic or traumatic retinal detachment. The former commonly presents itself as multiple giant cysts of various size located anywhere in the detached retina. Another category of environmental retinoschisis is the splitting of the retina due to traction of preretinal fibroplastic tissue in connection with so-called "massive vitreous retraction." A similar mechanism is responsible for intraretinal cleavage formation in cases of advanced diabetic retinopathy complicated by retinitis proliferans.

There are, of course, many other pathological conditions which can result in secondary retinoschisis or cysts: inflammatory processes, vascular diseases complicated by subclinical or intravitreal hemorrhages, metabolic retinopathies, blood dyscrasias, tumors, and so on.

The clinical significance of this secondary form of retinoschisis is important with regard to the prognosis in the individual case. The multiple giant cysts seen in long-standing retinal detachment can impose quite a problem during surgery since they may prevent an effective re-apposition of the retina. They usually require special techniques of treatment.

PATHOLOGY OF RETINOSCHISIS AND RETINAL CYSTS

This section is based on the study of pathologic specimens and autopsy eyes collected in the pathology laboratory of our department.

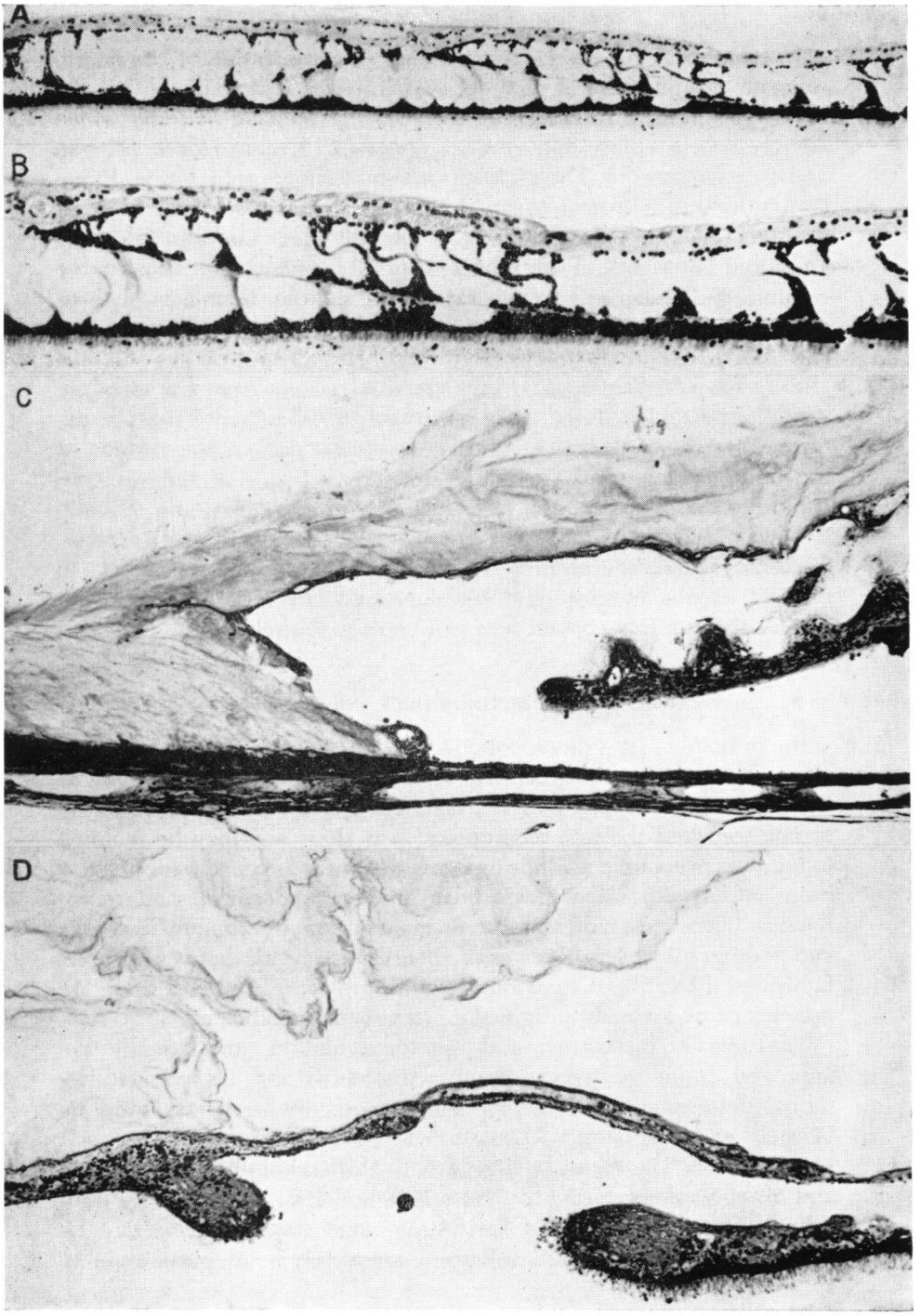
There is evidence that the retinoschisis in senile individuals develops from cystoid degeneration between the limiting membranes by pathological enlargement and coalescence of the so-called "Blessig's cysts"

or Iwanoff's retinal edema.[46-57] In exceptional cases the cysts involve the pars plana (Adams,[54] Okun[57]). In the beginning they are microcysts which preferentially develop in the outer plexiform layer separating the second and third neurons from each other.

However, this is not always the case as can be demonstrated by Figures 16A and 16B. This picture shows the development of retinoschisis by the confluence of microcysts originating in both the inner and the outer plexiform layers. The middle limiting membrane, recently described by Fine and Zimmermann,[58] separates both layers of retinoschisis. In some areas, one or the other of the two microcystic layers dominates, displacing the middle limiting membrane to direct contact with either the inner or the outer wall. Thus, the entire lumen of the schisis may be occupied by a cleavage confined either by the internal limiting membrane and residual "nerve fiber layer" on one side and the middle limiting membrane in unison with the outer limiting membrane on the other side, or by the external limiting membrane on one side and the middle limiting membrane adjacent to the internal limiting membrane and residual nerve fiber layer on the other side. In exceptional cases the splitting of the plexiform layers into two separate sections may be maintained throughout the entire area. The histopathologic differentiation as outlined above may have some significance with regard to the appearance and the behavior of certain forms of schisis and their response to therapy. The middle limiting membrane often disintegrates in which case the two layers of confluent microcysts coalesce to one large cavity. In the majority of cases, however, the outer wall is thicker than the inner wall as shown in Figures 16C and 16D. The exception to this rule is depicted in Figure 10, in which case the inner wall is thicker than the outer wall. The giant cyst on the right side of this photograph shows in addition a layer of microcysts in both walls. Although this observation presents theoretical evidence that a schisis of the retina may develop in three layers and more, clinical and histopathologic evidence almost invariably suggests the presence of only one or two cleavages within the retina.

FIGURE 16. SERIES OF PHOTOMICROGRAPHS PERTINENT TO RETINOSCHISIS.

A, alternate splitting of retina in inner and outer layers. H & E, ×90. B, same, larger magnification. C, retinoschisis in nerve fiber layer with condensation of the vitreous overlying the area of splitting. Arrow pointing at disintegration of retina in recess of the hyaloideo-orbicular space. D, retinoschisis in nerve fiber layer with detachment of the condensed vitreous overlying the area of retinal splitting. Notice breaks of outer walls in C and D. Regarding the spatial zone numbers see Figure 4. 4 = liquefaction of secondary vitreous. (Pictures C and D furnished by Dr. Okun)


A
B
C
D

In early cases the retinal tissue shows disorganization of the neural elements and increase of glial cells. This makes it very likely that the latter are the main producers of the tenacious mucoid material which fills the schisis cavity and which responds to hyaluronidase (Hogan and Zimmermann[60]). The pigment cells may show proliferation. Eventually the entire neural tissue disappears, leaving columns of compressed Mueller's cells and fibers as the only elements connecting the inner and outer wall of the schisis within its confinement. Finally, the columns of Mueller's fibers separate in the middle. Remnants of these columns remain attached to the inner side of both walls (Figures 16A and 16D). Ophthalmoscopically, these stumps appear as silk-like glittery formations rendering tiny specular reflexes from the interface with the mucoid material. It is important to differentiate these structures from the vitreoretinal fibrillar condensations on the surface of the retina which yield similar reflexes. Both forms of refleves contribute to the appearance of "frosting" or *état givré* of Gonin. Usually it is very difficult to make out the exact location of these structures. Such an endeavor requires excellent stereopsis and efficiency in indirect ophthalmoscopy and biomicroscopy. In certain cases Goldmann's three-mirror contact lens can be of great help.

TREATMENT OF RETINOSCHISIS AND GIANT CYSTS

In principle, the therapeutic approach in the management of idiopathic and peristatic forms of retinoschisis is the same. As long as the anatomical integrity and visual function of the eye is not seriously endangered and the rate of propression is slow, one may be inclined to take a conservative attitude as far as treatment is concerned. Regular examination with visual fields taken under standardized and reproducible conditions, and careful documentation by fundus drawings and photography every three or six months may be all that is advisable. However, if the visual function is significantly impaired and there are indications of a steady progression, treatment is indicated.

Transscleral diathermy and photocoagulation are among the approved forms of treatment of retinoschisis not complicated by retinal detachment. The former had successfully been employed by Pischel[31] and Utermann.[34] The latter was first suggested by the author[61] in May, 1962. The results achieved with this technique by the author and his co-workers during the years 1959 and 1963 were recently published (Okun, *et al.*[35]). Of forty-seven eyes treated exclusively by photocoagulation the schisis collapsed completely in 16, partially in 11

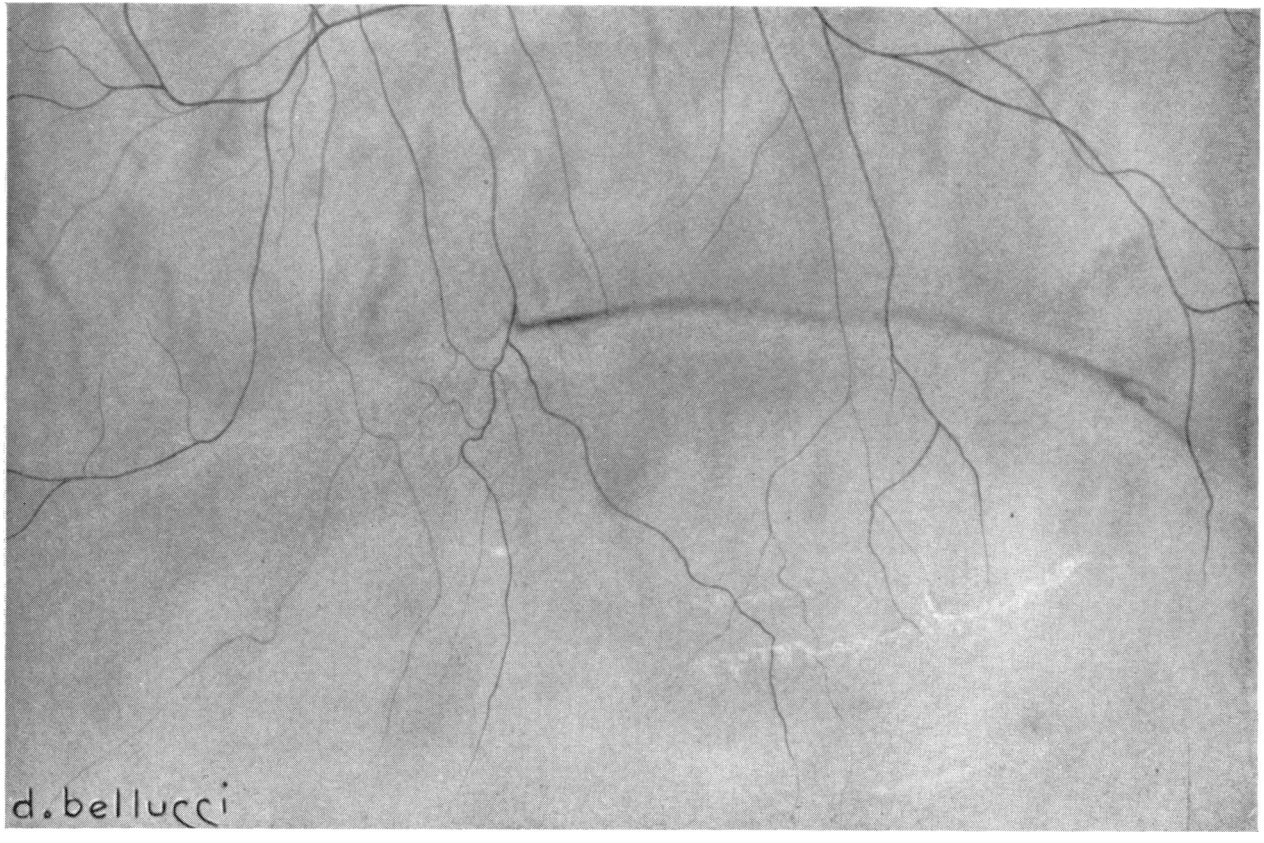


FIGURE 17. PAINTING OF INFERIOR RETINOSCHISIS WITH PARTIAL PIGMENTED DEMARCATION.

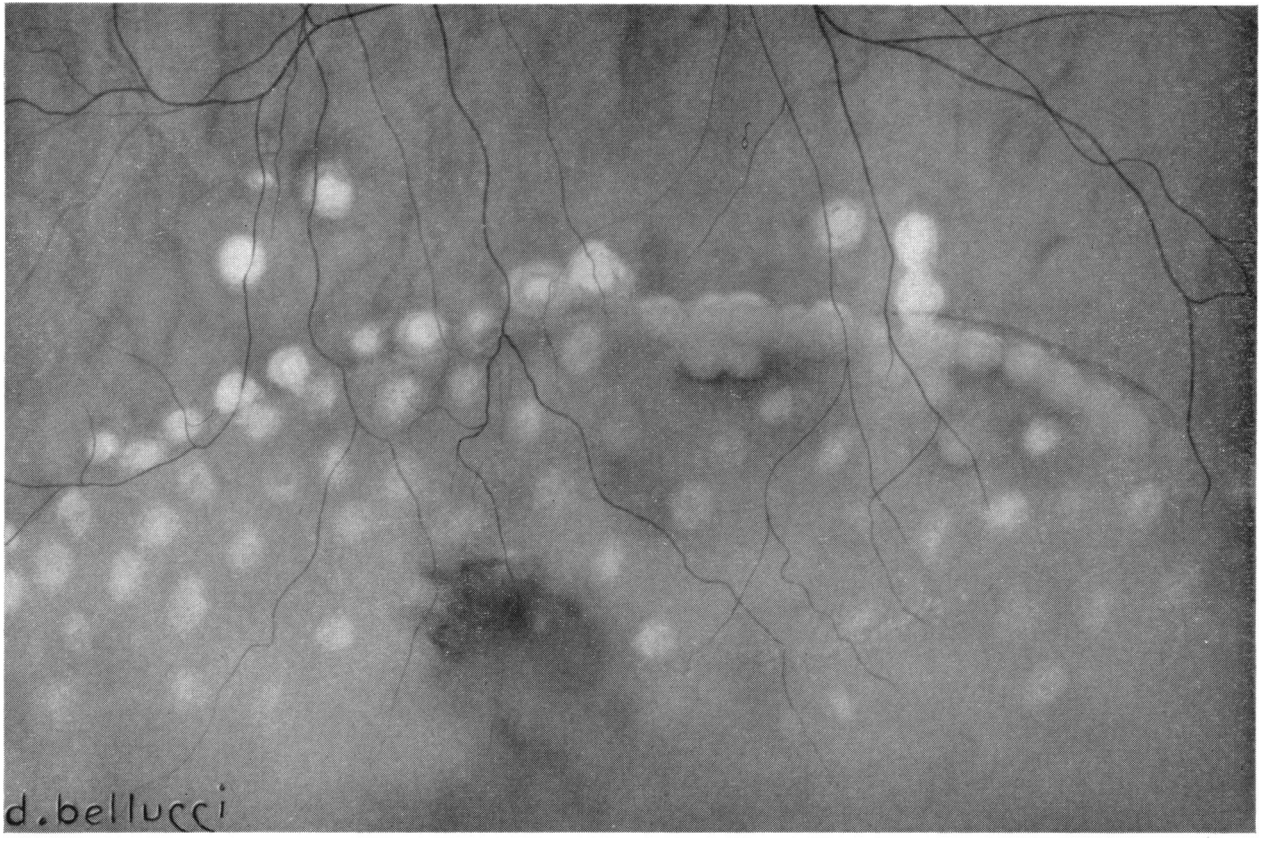


FIGURE 18. SAME AREA TWO DAYS AFTER PHOTOCOAGULATION.

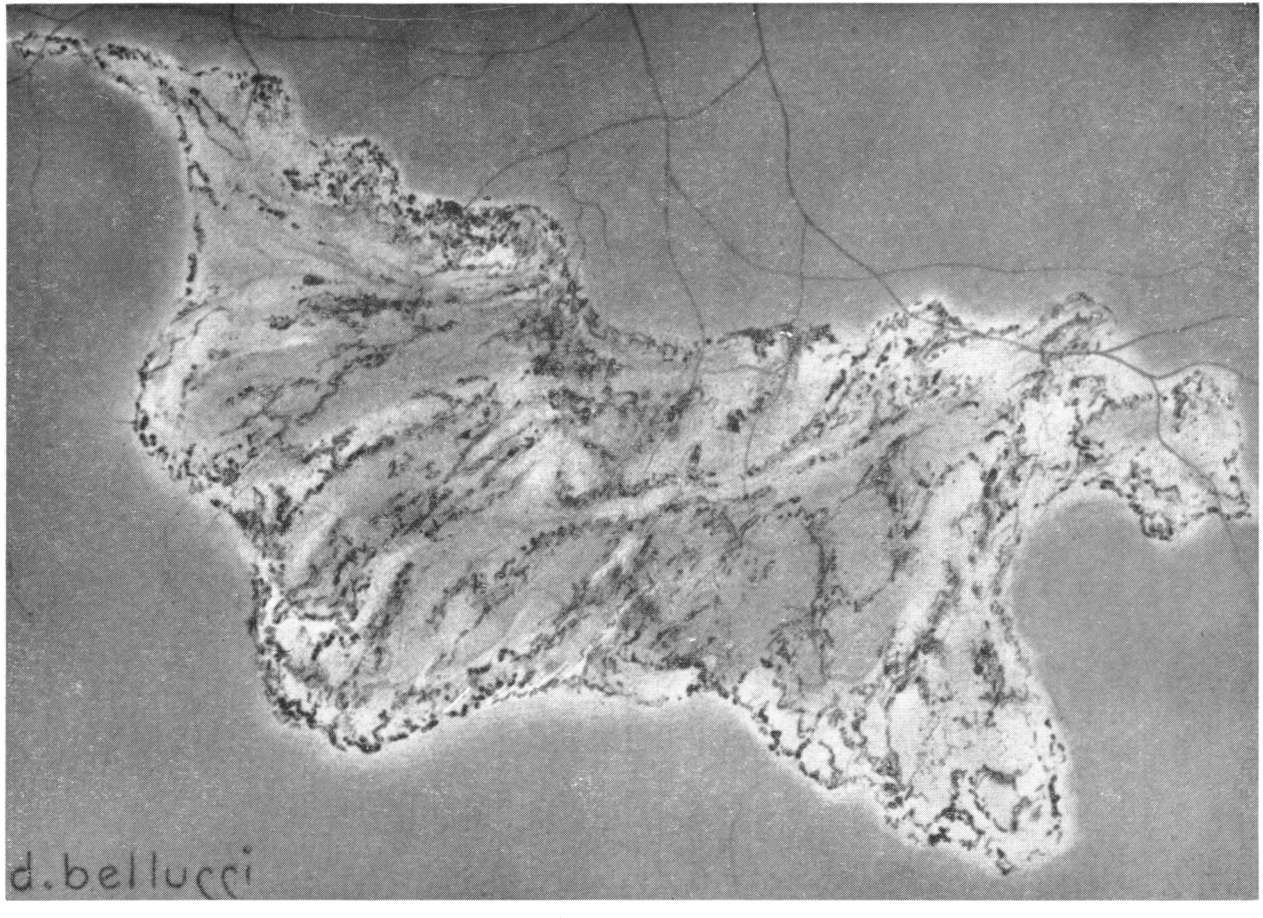


FIGURE 19. SAME AS FIGURES 17 AND 18, 4 WEEKS AFTER PHOTOCOAGULATION.

cases, and was effectively demarcated in 43 cases. In three cases it progressed despite treatment. Subsequent retinal detachment developed in one case. In this patient a scleral buckling procedure resulted in reattachment of the retina with complete collapse of the retinal cleavage. In many of the cases with incomplete collapse of the schisis we had the impression that the partial failure was due to incomplete treatment of the diseased area or to the fact that the effects were too mild in those places which remained split. Since then we have deliberately treated the schisic area with effects as strong as that depicted in Figure 5D. With this modification the percentage of complete collapse of schisis treated by photocoagulation exceeds 50 per cent.

In extensive cases several treatments may be required. As a rule, we do not cover more than one-third of the fundus at one time. The intervals vary from 8 days to 6 months. There is frequently an initial increase in the height of the schisis, followed by its gradual collapse. In a few cases we found that the retinal cleavage disappeared within five days although only half of the retinal cyst (Figure 13) or schisis had been treated. We have no explanation for this peculiar difference in the response of lesions to the treatment. Favorable results of treatment of retinoschisis by photocoagulation have also been reported by Pischel[31] and Guerry.[63]

In cases of retinoschisis complicated by retinal detachment we tend to operate on the detachment first and to treat with scleral diathermy those areas of the schisis which are easily accessible because of their peripheral location. If the schisis is very bullous, we attempt to evacuate the major portion of the fluid by aspiration from the area of cleavage and to transfer the aspirate to the preretinal space either *via* a large break or by re-entry at the pars plana next to the ora serrata. Photocoagulation is applied to the remaining areas of schisis at some later time.

In general, the results we have achieved with photocoagulation are more satisfactory than those obtained by diathermy. The appearance of the retina and choroid in a case of retinoschisis successfully treated with photocoagulation alone is shown in Figure 20.

DISCUSSION

The material presented indicates that there are four principal forms of idiopathic retinoschisis: (1) juvenile retinoschisis with gonosomal recessive transmission of inheritance; (2) juvenile retinoschisis with autosomal recessive transmission of inheritance; (3) juvenile bilateral

giant cysts based either on mutations or autosomal recessive transmission of inheritance; (4) presenile and senile retinoschisis with autosomal transmission of inheritance.

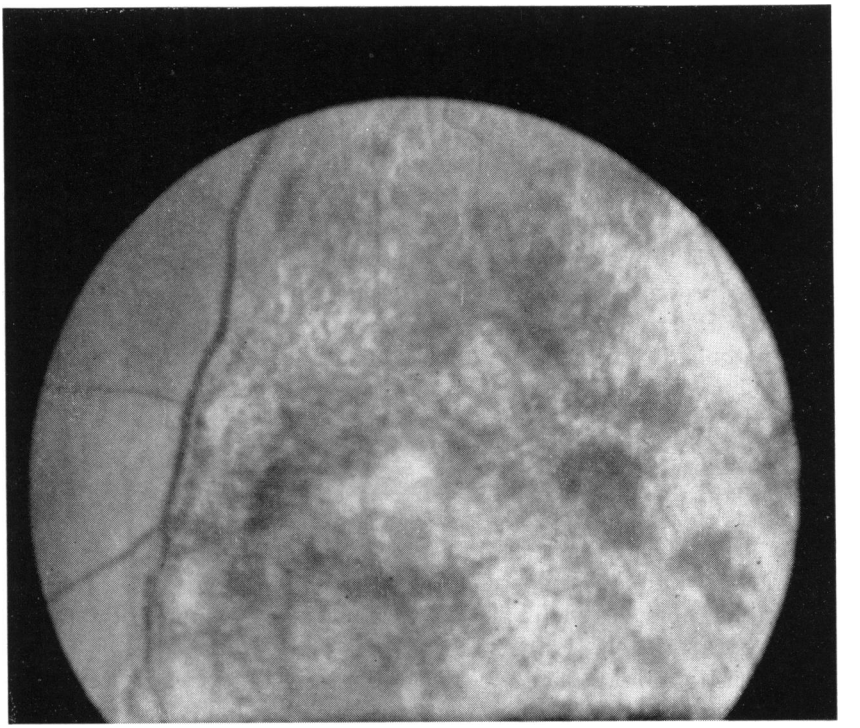


FIGURE 20. FUNDUS PHOTOGRAPH OF AREA OF RETINOSCHISIS 3 MONTHS AFTER COLLAPSE EFFECTED BY PHOTOCOAGULATION.

In contradistinction to the "congenital vascular veils of the vitreous" (Mann, *et al.*[8]). the development of retinoschisis and retinal cysts, as a rule, begins at a later stage of life. In typical cases of recessive sex-linked inheritance the first change observed is an altered appearance of the macula which displays pigment mottling of yellowish tint which gradually assumes a star-shaped configuration centered around the fovea (Figure 5A) as the retinal splitting begins and progresses to the typical picture as shown in Figures 1, 3, and 5. Slight deviations from this initial phenotypic manifestation of the disease are seen in those cases in which the cleavage of the retina is minimal and remains

limited to the inferior temporal quadrants of the globe. With the macular changes are associated depression of the central vision, relative central scotomata, and absolute fie'd defects in the periphery corresponding to the area of retinal splitting. However, in a few cases of definite retinoschisis evidently involving the innermost layers of the retina, residual function was retained within the depressed field of vision.

The gonosomal form of schisis is usually associated with hyperopia and affects only males. Female descendants of afflicted fathers are carriers, who can produce a homozygotic female offspring only by marriage to a man phenotypically afflicted by this disease. This possibility cannot completely be ruled out in the case of the twin sister to which Figures 7 and 8 refer. For the probands related to the pedigree presented in Figure 11, this possibility could be ruled out since the brother of the afflicted three sisters did not show any pertinent pathology. Furthermore, no other form of idiopathic retinoschisis but the one with gonosomal recessive transmission of inheritance showed the characteristic macular changes described above.

The slow progression of the schisis in early and even in advanced cases can be explained by the protective layer of formed vitreous over the area of retinal cleavage. It is difficult to say whether this condensation is the result of compression of the collagenous frame in the vitreous by the extending schisis or whether it represents a reactive production of collagenous fibers by irritated cel's of the vitreoretinal border structures. As long as the vitreoretinal border structures maintain their continuity and integrity, the expansion of the retinoschisis is scarcely noticeable.

Many outstanding ophthalmologists consider retinoschisis a stationary disorder which does not require any treatment. However, it is now well recognized (1) that schisis can spread both circumferentially and posteriorly to endanger the macula (12 out of 60 among our own cases) and (2) that schisis can develop into retinal detachment. This transformation, which occurs in at least 20 per cent of all schisis cases, commences when the vitreous liquefies and the hyaloid membrane detaches over the area of cleavage. Breaks of the outer and inner layer may form by mere disintegration of the retinal tissue. As long as the condensed vitreous does not separate from the retina, significant retinal detachment does not occur. However, if the vitreous separates from the inner wall as shown in Figure 16D, liquefied vitreous usually gains access to the subretinal space and a retinal detachment may form. Theoretically, there are other possibilities

which may lead to retinal detachment without disruption of the inner wall of the retinal cleavage. First, a ballooning cyst, as depicted in Figure 9, can cause a compact break of the retina with the anterior hyaloid firmly attached, a mechanism recognized by Weve.[37] Secondly, the retina may begin to split or disintegrate in the recess of the hyaloideo-orbicular space at the oral junction as depicted in Figure 16C.

The source of the mucoid material in the cavity of microcysts and retinoschisis is not known. The circumstances which incite, accompany, and modify the mucoid production are also unknown. The evidence is overwhelming that genetic factors play a decisive role in the idiopathic cases of retinoschisis and perhaps also in those cases in which cystic changes precede a retinal detachment. In the very advanced cases of retinoschisis all the neural elements of the retina and the entire pigment epithelial layer in the area of schisis may disappear. Eventually only glia cells including Mueller's cells remain. In such cases, there are no cellular structures other than the glia cells which could be blamed for the production of the mucopolysaccharides in the cavity of the schisis. It is unlikely that the pigment epithelial cells are directly responsible for the mucopolysaccharide production, since they are often absent in the area where the retina has split, whereas the pigment cells are sometimes piled up underneath the more normal neural structure. Teng[62] offered the suggestion that cystoid degeneration and schisis of the retina result from the degenerative "effect of vitreous on nerve fibers." He bases his concept on the observation that the vitreous body "as well as aqueous" exerts a lytic effect on collagen and nerve fibers. However this explanation does not take into account that in typical cases of retinoschisis the vitreous is condensed in the area overlying the schisis thus protecting the retina from vitreous humor.

Another significant point in the pathogenesis of giant cysts and retinoschisis is the observation that the walls confining the macrocysts and cavities of retinoschisis bulge toward the vitreous, and the subretinal space, when the retina is detached. This indicates that during the period of retinal splitting the pressure in the cleavage must be higher than in the vitreous and the subretinal space. Also, it is interesting to note that in cases of retinoschisis which develop prior to retinal detachment, the inner wall is frequently thinner than the outer wall, whereas in cases of retinal detachment which antecede the developing of the retinoschisis or giant cyst, this relation is reversed, e.g., the outer wall is thinner than the inner wall. It may be assumed that at

arrest of the pathogenetic activities the hydrostatic pressure in the schisis cavity and within the surrounding structure is essentially the same. Of course, during the period of expansion the production of mucoid material and its decomposition cannot be expected to be in equilibrium. It may be conjectured that photocoagulation exerts its beneficial effect on retinoschisis by changing this equilibrium in favor of decomposition and resorption. This could be achieved (1) by destruction of the cells responsible for the production of the mucoid material and (2) by thermogenic degradation of the mucopolysaccharides, thus resulting in faster absorption. Finally, there is the possibility that the heat effect produced during photocoagulation weakens and eventually ruptures the outer wall. The degraded mucoid material can then readily be expelled into the subretinal space and absorbed by the choroidal vasculature. The pull of the condensed vitreous on the surface of the retina may be an essential pathogenetic factor in those cases which do not respond to photocoagulation or diathermy treatment.

The angiopathy present in all typical cases of juvenile hereditary schisis observed has also been seen in patients with presenile and senile retinoschisis, although to a lesser degree. It seems to bear some significance regarding the pathogenesis of this disease. In this connection it is interesting that Scorciarini-Coppola and coworkers[25] discovered a "minimal prothrombin Factor 7 deficiency" associated with increased capillary fragility and liver function abnormality in one of two affected siblings. Balian and Falls[26] found an inconclusive but suggestive state of "thrombocytopathy" in one of their cases. Kahán, *et al.*,[67,68] in 1963 reported erythrocytic anomalies in form of acanthosis in hereditary vitreoretinal degeneration of Wagner, in which retinoschisis was present, and in cases of Eales's disease. Both conditions showed vaso-obstructions as described by Scorciarini-Coppola, *et al.*[25] These observations suggest that the vaso-obstructive conditions observed in our cases of retinoschisis may be based on similar hematopathic and angiopathic changes. Further investigation of these aspects of the disease is needed.

SUMMARY

A discussion of the essential clinical, pathologic, and therapeutic aspects of retinoschisis and giant cysts is presented.

The analysis of nearly 200 pertinent cases, including two pairs of identical twins, permits the distinction of four phenotypically different

groups of idiopathic retinoschisis with either gonosomal or autosomal recessive transmission of inheritance. The concordant findings are differentiated from discordant changes which are of a secondary nature, probably based on environmental factors.

Evidence is presented that a significant number of patients with retinoschisis develop retinal detachment. The pathogenesis of this complication is associated with the separation of the condensed vitreoretinal border structures from the retina in the area of retinal splitting.

The methods of treatment are empiric. Diathermy or photocoagulation of the entire outer wall of the retinal cleavage has proved to be effective. The understanding of the basic mechanism effecting the obliteration of retinoschisis and retinal cysts is conjectural.

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