FAMILIAL EXUDATIVE VITREORETINOPATHY

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ABSTRACT

Purpose: To evaluate the natural history of Familial Exudative Vitreoretinopathy (FEVR) with emphasis on the effect of the age of onset on its severity and on the development of late complications such as cataract and retinal detachment. Also, to evaluate affected patients for DNA abnormalities.

Methods: The records of thirty-nine patients with FEVR were studied. All were asked to come in for a final follow-up examination. The referring physician was asked to provide the latest findings for those who could not. On 10 patients, karyotypes were prepared.

Results: Only 2 of 28 patients whose onset of symptoms was prior to their third birthday had a final visual acuity of 20/200 or better. Older patients had a better prognosis, because they were more likely to have asymmetrical retinal deterioration with only one eye deteriorating. Preservation of good visual acuity into the teens and later was no guarantee that deterioration would not occur. In 3 eyes of 4 patients who were asymptomatic until 15 years of age, the final visual acuity was counting fingers or worse. In 5 patients, retinal detachment developed 6 to 17 years after apparent stabilization. The karyotype of 10 patients showed no evidence for rearrangement, altered size, translocations or deletions of chromosome 11 or any other chromosome. Of the 31 eyes in patients older than 15 years, 10 (32%) had a significant cataract. Three eyes underwent cataract surgery.

Conclusions: The prognosis for infants with FEVR is extremely poor and the long-term prognosis for patients with a later onset of the condition is guarded. Retinal detachment, macular dragging, and cataract are common late complications which can develop even in patients whose eye findings appear to be stable. Karyotype studies ruled out involvement of chromosome 11 or others at a gross level, but did not exclude them at the location for some genetic defect related to FEVR because single base changes and small deletions or insertions may be undetectable by the methods utilized.

INTRODUCTION

Familial exudative vitreoretinopathy (FEVR) was first described in 1969 by Criswick and Schepens.[1] Their six patients, from two families, had fundus

changes remarkably similar to those seen in retinopathy of prematurity (ROP), but the patients were children and adolescents who were born after full-term pregnancies, who had normal birth weight, and who had no respiratory distress or oxygen therapy. Like patients with ROP, these patients had bilateral involvement with peripheral neovascularization. Thick fibrovascular vitreous membranes pulled on the retina, dragging the macula temporally and distorting the optic disc. Many affected eyes underwent slowly progressive deterioration with peripheral subretinal and intraretinal exudation and exudative and traction retinal detachment. In some eyes, the exudative component of the retinal detachment was so severe that the condition resembled Coats' disease. Other findings included abnormal retinal branching, pseudoexotropia secondary to macular ectopia, falciform folds, rhegmatogenous retinal detachment, and, occasionally, marked asymmetry.

Subsequent reports have increased our understanding of this condition. In 1971, Gow and Oliver[2] carefully examined the families of affected patients and concluded that the inheritance pattern was autosomal dominant. In 1976, Canny and Oliver[3] used fluorescein angiography to demonstrate abrupt cessation of the peripheral retinal capillary network. They suggested that the primary abnormality is cessation of growth of the peripheral small blood vessels before they were able to vascularize the periphery. Other investigators[4-6] subsequently verified these fluorescein angiographic findings.

Since these early reports, many other articles on FEVR have been published.[7-39] It is the purpose of this thesis to present findings not previously stressed in the literature as well as the natural history of the disorder based on long-term follow-up of affected patients. In so doing, the study will compare the course of FEVR in infants and adults with that of ROP and other entities that simulate FEVR. The importance of recognizing FEVR as a lifetime disease that may progress after apparent stabilization will be demonstrated, as will the finding that cataract and retinal detachment are late complications. It will show that the value of treatment remains unproved. Finally, it will evaluate several patients for DNA abnormalities.

REVIEW OF THE LITERATURE

CLINICAL FINDINGS

Mildly Affected Patients

A peripheral zone of avascular retina is the sine qua non for the diagnosis of FEVR. Van Nouhuys[7] found this abnormality in 100% of affected patients in whom the periphery could be examined. In many patients, this may be FEVR's only manifestation. Usually, the avascular zone is confined to the temporal periphery, but it may extend for 360°.[8,9] In 81% of mildly affected eyes, it has a "V" shape with the apex of the "V" located in the horizontal

meridian and aimed posteriorly.[10,11] The avascular zone can frequently be seen by indirect ophthalmoscopy alone, but detection is facilitated by using a green filter in front of the light source of the indirect ophthalmoscope. The resultant red-free light emphasizes the color difference between the vascularized and nonvascularized retina.[8] Fluorescein angiography also clearly shows the border between these areas.

There is often excessive branching of the retinal blood vessels, giving rise to an increased number of peripheral blood vessels. The angle between the branches is very narrow, so they often follow a nearly parallel course. Near the avascular zone, they may have a fibrillar or brushlike appearance. At the border of the avascular zone, arteriovenous shunt formation is common and the peripheral retinal vessels may be dilated and sheathed. The blood vessels in the posterior pole are also frequently abnormal. Even in the mildest cases with no evidence of vitreous traction, the vessels may show an unusual temporally bent course and often are associated with leakage on fluorescein angiography.

Moderately Affected Patients

Although FEVR can cause blindness, most affected patients show no progression even though they may have a peripheral avascular zone extending posterior to the equator. For reasons that are not clear, a minority of patients develop hyperpermeable blood vessels, neovascularization, and increasing vitreous traction.

An abnormally strong vitreoretinal adhesion has been found in 41% of affected eyes, and the anterior hyaloid just behind the lens is frequently thickened.[10] Vitreous adhesion with subsequent traction is the most common cause of severe visual loss. In most eyes, the initial manifestation of vitreoretinal traction is macular ectopia, which is seen in 18% to 49% of affected eyes.[10,12] In others, the initial change is the development of intraretinal and subretinal exudates.[12] An uncommon manifestation of traction is peripheral retinoschisis, which is seen in 4% of patients.[12]

In some eyes, peripheral traction and/or exudative retinal detachment develops. It is difficult to classify traction and exudative retinal detachment separately in FEVR, because in many cases of traction retinal detachment there is a prominent exudative component. In contrast, all cases that are predominantly exudative have prominent traction. For the remainder of this thesis, this presentation will be referred to as nonrhegmatogenous retinal detachment.

Miyakubo and associates[10] reported that nonrhegmatogenous retinal detachment was present in 17% (23/133) of the eyes in his series. Frequently the detachment remains in the periphery, but occasionally it may spread rapidly to involve the macula. Fortunately, for many patients posterior progression never occurs or is slow.[5,7] It must be stressed that progression of FEVR may spontaneously cease at any point. Van Nouhuys[7] reports

that only a few peripheral nonrhegmatogenous retinal detachments progress. Ober and colleagues[5] reported a case in which a peripheral traction retinal detachment did not progress posteriorly for 14 years.

Extraretinal Neovascularization: Extraretinal neovascularization has been reported in as many as 11% to 20% of eyes.[11,12] When present in children, neovascularization is reddish in color; in older patients, it appears to be more fibrotic.[12] It may be the source of a vitreous hemorrhage.

Some investigators[11,13] have reported that neovascularization is a bad prognostic sign. Miyakubo and associates[11] found that patients with neovascularization were much more likely to have dragging of the retina than patients without it. Van Nouhuys[7] feels that neovascularization is not commonly found in older patients because when it develops, it usually precipitates total vitreous organization and cannot later be recognized.

Neovascularization does not always portend severe deterioration. Gitter and coworkers[14] reported 5 patients with attached retinas and neovascularization whose ages were 6, 11, 33, 41, and 65 years. After 2 years of follow-up, none progressed. Similarly, Feldman and associates[15] reported a 67-year-old patient with no light perception and a total retinal detachment in one eye and 20/30 vision and a large frond of neovascularization in the other eye. Ober and colleagues[5] found neovascularization in the eyes of patients who were 15, 17, and 22 years old. Van Nouhuys[7] also reported three patients from 20 to 40 years of age who had small areas of neovascularization and flat retinas.

Severely Affected Patients

In some patients, the disc and retina are dragged temporally, causing a falciform fold that radiates from the periphery to the optic disk. Dudgeon[16] was the first to suggest that many of the eyes previously felt to have idiopathic falciform fold probably had FEVR. Others later confirmed this.[17,18] Severe vitreoretinal traction can progress to cause a total nonrhegmatogenous retinal detachment. In some cases, the exudation is so severe that FEVR can be mistaken for Coats' disease.

In FEVR, nonrhegmatogenous retinal detachment is more common in children and adolescents than in adults. Miyakubo and associates[10] found only one case in patients older than 19 and none in patients older than 30. In the most severe cases, a fibrovascular membrane extends from ora serrata to ora serrata across the posterior surface of the lens. As previously mentioned, neovascularization seems to initiate the vitreous shrinkage and traction and retinal detachment, but nonrhegmatogenous retinal detachment occurs almost as commonly in eyes in which neovascularization is absent.[7]

Rhegmatogenous retinal detachment is a common complication of FEVR, being reported in 8% to 32% of patients.[10,12] Indeed, Miyakubo and associates[11] found it in 11 of 34 patients affected with FEVR. They esti-

mated that 12% of all patients under 30 years of age with rhegmatogenous retinal detachment had FEVR. The causative breaks most commonly are small round holes in avascular retina,[7] but horseshoe, and even giant, tears have been reported.[6,7,12] Miyakubo and colleagues[10] found rhegmatogenous retinal detachment in no patients younger than 10 years of age. It was most commonly found in patients between the ages of 10 and 20 years. One affected patient was 50 years old.[10]

PROGRESSION FOR DIFFERENT AGE-GROUPS

The most rapid progression is seen in children and adolescents.[7,8,13] In children under 10 years of age, nonrhegmatogenous retinal detachment and falciform fold are the most common causes of visual loss. Several infants have been reported to have total blindness from retinal detachment in the first months of life.[7,8,18] Tasman and associates[8] reported a 6-year-old patient whose vision was well documented to deteriorate from 20/20 to counting fingers over a 4-week period because of severe vitreoretinal traction with retinal dragging. Rapid progression can also occur in adolescents. Dudgeon[16] reported an 18-year-old patient whose vision deteriorated from 20/40 to 4/60 in 1 month. Van Nouhuys[7] reported a similar case.

A typical case of slow progression was described by Slusher and Hutton.[13] A 7-year-old patient had a visual acuity of no light perception in the right eye and 20/60 in the left. Nineteen years later, at the age of 26, her vision had decreased to 20/400. She had a posterior subcapsular cataract, neovascularization, dragging of the macula, and nonrhegmatogenous retinal detachment.

As already mentioned, if patients with FEVR do not suffer deterioration before they are 20 years old, their ocular findings and visual acuity usually remain stable with retention of useful vision.[2,5,8,15] Feldman and associates[15] reported 8 affected patients, of whom 7 were between 17 and 67 years. All 7 had acuity of 20/30 or better in one eye, and 6 had 20/20 vision or better in one eye. Van Nouhuys[7] reported that among 72 patients with evident FEVR, 59 (82%) had visual acuity in one eye better than 20/40. The visual acuity in the better eye was 20/100 or worse in only 11% (8 of 72). Saraux and colleagues[19] also reported a large pedigree in which progression was rare in patients over 20 years. Tasman and associates[8] reported 15 cases, of which 73% were in a stable asymptomatic form. The eyes that progressed to retinal detachment did so before the patients were 10 years old. The main cause of decreased vision after the age of 30 years is rhegmatogenous retinal detachment, but this is rare.[7]

Although bilateral involvement is the rule in FEVR, the severity is frequently very asymmetric. Several investigators[7,8,15] have described patients whose vision was reduced to light perception in one eye but who retained 20/30 vision or better in the other.

ANTERIOR SEGMENT FINDINGS

There is no characteristic refractive error in FEVR. In the series of Van Nouhuys, 101 of 126 eyes had a refractive error between +3 and -3 diopters. However, because 12 eyes had a refractive error of -6 diopters or greater, refractive error cannot be used with certainty to differentiate FEVR from ROP.[20] Anisometropic amblyopia is relatively common, being reported in 13% of a large series.[12] Posterior subcapsular cataracts at ages 16, 26, and 36 years have been reported, but early cataract is not felt to be a characteristic finding.[7,13,21]

SYMPTOMS

Approximately one half of all patients with FEVR are asymptomatic, the diagnosis being made when families of patients with suspected or known FEVR are screened. In a few patients, diagnosis is made on routine examination. In most infants, FEVR is diagnosed when they are evaluated for failure to fix and follow objects or lights, for pendular nystagmus, or for heterotropia. In occasional cases, a total retinal detachment or significant lipid exudation may cause leukokoria.[9]

The diagnosis is made in children and adults when they notice decreased vision, the most common cause of which is retinal detachment. Decreased vision may also be caused by temporal dragging of the macula, but even if the macula is ectopic, the patient may have normal vision.[15] Finally, in some patients, the diagnosis is made during evaluation for pseudoexotropia. Temporal displacement of the macula causes a positive kappa angle in 25% of eyes with FEVR.[7] Such eyes appear to be exotropic, but the patient is orthophoric on cover/uncover testing.

FLOURESCEIN ANGIOGRAPHY

As already mentioned, fluorescein angiography made a major contribution to our understanding of FEVR. In 1976, Canny and Oliver[3] studied patients with moderately advanced disease. They found an abrupt cessation of the retinal capillary network in a scalloped edge posterior to fibrovascular proliferations. The capillaries at the edge of the vascularized retina leaked fluorescein. Their findings suggested that the primary abnormality in FEVR was failure of peripheral small blood vessels to progress to the ora serrata. Others have since confirmed and added to their landmark study. Laqua[6] pointed out that what others thought to be white without pressure was actually avascular retina. Nijhuis and associates[4] and Ober and colleagues[5] independently enlarged upon the findings of Canny and Oliver by studying patients, many of whom were asymptomatic relatives of visually affected patients, in the earliest stages of the condition. Ober described the "brush border" formed by the small blood vessels at the border of the avascular zone.[5] Nijhuis felt that the four most important features of fluorescein angiography in asymptomatic patients are dragging of perimacular capillar-

ies toward the temporal periphery, dilation of perimacular capillaries with slight leakage, peripheral arteriovenous shunts with occasional leakage just proximal to the avascular zone, and abrupt cessation of capillaries.[4] Finally, Feldman and coworkers[15] described cystoid macular edema.

RETINAL PHYSIOLOGY

The electroretinogram, electro-oculogram, color vision testing, and visual fields are normal or only mildly abnormal in patients who have only mild manifestations of FEVR.[7,15,22]

INHERITANCE

The gene for FEVR is characterized by marked variation of expressivity. Whereas for many patients FEVR is a blinding disorder, approximately one half of affected patients are asymptomatic with minimal clinical findings.[2,4,7,8] In early papers on FEVR, many minimally or mildly affected individuals were omitted from analysis because they were considered to be unaffected. Now, however, examination of the periphery with red-free light and fluorescein angiography permits detection of nearly all cases. Gow and Oliver[2] first demonstrated autosomal dominant inheritance, and many other investigators[4-6,8-10,14,19,24] have confirmed their findings. Males and females are equally affected, with father-to-son transmission. The penetrance has been estimated to be between 91% and 100%.[5,7] Linkage analysis of patients with autosomal dominant inheritance suggests that the gene locus is on the long arm of chromosome 11.[25,26]

Although in most families FEVR is transmitted as an autosomal dominant trait, other inheritance is possible. Plager and associates[27] reported a pedigree with X-linked inheritance. In this family, 4 of 7 males who were examined were affected and none of 12 females. All affected males were related through female relatives. The investigators reanalyzed a pedigree reported by Criswick and Schepens[1] and concluded that its inheritance was probably X-linked, because 5 of 8 males and none of 6 females were affected and because all affected males were related through their mothers and other female relatives. Similarly, they suggest that Dudgeon's pedigree[16] was X-linked. Recently, Fullwood and associates[28] reported DNA linkage analysis that confirmed Plager's analysis. Studying Dudgeon's pedigree, they localized a gene locus at either Xq21.3 or at Xp11. Since this region includes the locus for the gene for Norrie's disease, they suggest that this disease and FEVR are allelic. Further analysis of Dudgeon's pedigree by Chen and associates[29] found a missense mutation in the Norrie gene locus (NDP) gene, which caused a neutral amino acid substitution, suggesting that phenotypes of both X-linked FEVR and Norrie's disease can result from mutations in the same gene. Others have also presented genetic evidence for an X-linked inheritance.[30,31]

Finally, authorities on FEVR who are familiar with all of the well-recog-

nized findings and the differential diagnosis have reported sporadic cases. Miyakubo and associates[11] studied 77 cases, of which 16 were felt to be sporadic. Van Nouhuys[12] reported 90 cases, of which 5 were sporadic.

ETIOLOGY

Originally thought to be caused by a vitreous abnormality that resulted in severe subsequent traction,[1,2] FEVR is now considered to be caused by an abnormality in small blood vessels that prevents them from completing vascularization of the periphery.[6,7,21] The best evidence for this view is that all affected patients have a peripheral avascular zone, but only 56% of 180 eyes studied have apparent vitreous lesions.[12] This strongly suggests that the vascular changes are primary and the vitreous changes are secondary. Van Nouhuys[7] points out that the normal fetal retina at 2 to 3 months shows a V-shaped marginal zone of immature vascular tissue resembling that seen in FEVR. He feels that the pathogenesis of the FEVR is based on premature arrest of the vascular development of the retina in the last trimester. He speculates that the abnormal gene causes a metabolic disorder that is limited to the complex of peripheral vasoformative tissue.

HISTOPATHOLOGY

Thus far, no eyes examined histopathologically have been in the early stages of the disease. All have had far advanced deterioration. Boldrey and associates[21] examined two eyes enucleated for angle-closure glaucoma. In one, this was caused by sudden massive subretinal hemorrhage with rotation forward of the iris-lens diaphragm. In the other, it was caused by neovascularization of the iris. Posterior segment findings included total retinal detachment, peripheral retinal vascular proliferation, and fibrovascular preretinal membrane formation. Nicholson and Galvis[23] also examined an eye enucleated because of neovascular glaucoma. They found a focal nodular zone of fibrovascular proliferation, necrosis, and acute inflammation within the temporal pre-equatorial retina associated with dense preretinal fibrous organization. Brockhurst and associates[32] examined two eyes enucleated from twins with presumed FEVR. (Other family members could not be examined.) They found total retinal detachment and preretinal membranes. Finally, van Nouhuys[7] examined an eye enucleated 6 weeks after birth because of suspected possible retinoblastoma. He found a total retinal detachment with a dense preretinal membrane and extensive hemorrhage in the retina. There was a fibrous plaque behind the lens.

PLATELET ABNORMALITIES

Chaudhuri and associates[33] found decreased platelet aggregation in FEVR patients, especially when it was tested for by induction with a low concentration of arachidonic acid. They speculated that this may lead to decreased production of thromboxane A2, which has a protective role on immature

retinal blood vessels. Others, however, have been unable to confirm his findings.[7,34-36]

TREATMENT

Since FEVR has such a variable course, only patients at high risk of progression should receive treatment. Characteristics generally agreed upon to identify such patients are severe traction on the retina with retinal detachment and neovascularization of the retina.

Cryotherapy and Photocoagulation

The initial attempts to treat FEVR were directed at eliminating the peripheral neovascularization. Criswick and Schepens[1] used both photocoagulation and cryotherapy to treat a 4-year-old; nevertheless, the patient had increasing hard exudates over the next 2 years. Two other patients developed a rhegmatogenous retinal detachment shortly after the treatment. Gow and Oliver[2] used cryotherapy to treat areas of neovascularization directly. Four treated patients were observed for 8 months, and all showed atrophy of the fibrovascular cicatrix and occlusion of the feeder vessels. One patient who was treated with photocoagulation was stabilized for 12 months. Others have reported arrest of progression after cryotherapy or photocoagulation. Tasman and associates[8] and Dudgeon[16] successfully prevented progression of exudative retinal detachments with cryotherapy, but shortly after cryotherapy in one of Dudgeon's cases, a total retinal detachment with a new dialysis developed. Feldman and colleagues[15] stabilized an eye with neovascularization with cryotherapy. Canny and Oliver[3] treated a 15-year-old who had neovascularization and exudative retinal detachment with cryotherapy. The patient remained stable for 4 years. Van Nouhuys[7] reported good obliteration of neovascularization with xenon arc or laser photocoagulation in 3 patients.

Scleral Buckling Procedures

Rhegmatogenous Retinal Detachment: As previously mentioned, rhegmatogenous retinal detachment is most common in patients from 10 to 20 years of age, but may be seen in patients as old as 50. In general, the prognosis for successful repair is excellent. Despite the strong vitreoretinal traction, vitrectomy is usually not required. Criswick and Schepens[1] were the first to successfully repair a rhegmatogenous retinal detachment with a scleral buckling procedure. Others have also been successful with good visual results.[6,7,16]

Nonrhegmatogenous Retinal Detachment: Crock was cited by Ober to be the first to use a scleral buckling procedure to repair a nonrhegmatogenous retinal detachment.[5] Others have also had good results.

Bergen and Glassman[37] treated a 15-year-old with a scleral buckling procedure for an inferior nonrhegmatogenous retinal detachment. The retina

was reattached, and visual acuity improved from 20/50 to 20/30.

Plager and associates[27] used a scleral buckling procedure and cryotherapy to treat a 3-year-old with early vitreous traction and exudative retinal detachment. The patient did not have neovascularization. The condition stabilized.

Van Nouhuys[7] reported flattening of a nonrhegmatogenous retinal detachment with a scleral buckling procedure. The patient was 17 years old at the time of the surgery. The lengths of follow-up and visual acuity were not given.

Feldman and associates[15] reported a 39-year-old patient with neovascularization and a peripheral traction retinal detachment who over the subsequent 2 years progressed to a total retinal detachment. A scleral buckling procedure combined with vitrectomy failed to reattach the retina.

An unusual complication was reported by Okubo and associates.[38] Three months after a successful scleral buckling procedure, a 16-year-old boy developed severe panuveitis in both eyes, accompanied by a bullous nonrhegmatogenous retinal detachment. Treatment with high doses of systemic corticosteroids caused reabsorption of the subretinal fluid.

Vitrectomy

Treister and Machemer[39] were the first to use vitrectomy to treat retinal detachment caused by FEVR. By releasing vitreous traction, they repaired a nonrhegmatogenous retinal detachment in a 16-year-old girl who complained of progressive loss of vision for 1 year. Her vision improved from 20/60 to 20/30.

Bergen and Glassman[37] treated an 11-year-old with a vitrectomy/lensectomy scleral buckling procedure for an inferior traction retinal detachment with macular involvement. The procedure failed.

The prognosis for successful repair of retinal detachment is much better in patients 19 years and older than in younger patients.[12] Van Nouhuys[12] reported a series of 14 eyes with retinal detachment that underwent 22 operations by various surgeons. It was not specified how many detachments were rhegmatogenous and how many were nonrhegmatogenous. Seven of the 14 detached retinas were successfully reattached by 5 scleral buckling procedures and 2 vitrectomies. Ten vitrectomies and 3 scleral buckling procedures were unsuccessful, despite the use of silicone oil in 6 operations. All operations on patients younger than 19 were unsuccessful, whereas all operations on eyes of patients older than 19 years were successful. The reason for this marked discrepancy was that proliferative vitreoretinopathy occurred much more commonly in the younger patients. His series also suggests that eyes that require vitrectomy have a poor prognosis.

MATERIALS AND METHODS

The data base for this study was constructed from the records of the follow-

ing groups of patients. There were 39 patients with FEVR who belonged to 22 families. Eighteen were females and 21 were males. There were 120 patients with ROP who were examined after they were 16 years of age or older. These patients will be designated as having "adult ROP" for comparison with older patients with FEVR. Finally, there were 80 consecutive infants treated with laser photocoagulation or cryotherapy for ROP, 6 infants with retinal dragging caused by X-linked retinoschisis, and 6 patients with incontinentia pigmenti.

A careful history of ocular and systemic disease, as well as a family history, was taken in all cases. Family members were asked to come in for examination. Infants who could not cooperate were examined under anesthesia. The anterior segment was examined with the operating microscope. Corneal diameters were measured. The intraocular pressure was measured with Schiotz tonometry. The fundus was examined with indirect ophthalmoscopy, with and without red-free light, and with scleral depression. In many cases, fluorescein angiography was performed by using a portable unit.

In children and adults, Snellen visual acuity was measured. The anterior segment was examined by slit-lamp biomicroscopy. Applanation tonometry was used to measure the intraocular pressure. The posterior pole was examined by using a contact lens, a Hruby lens, or a 60- or 90-diopter handheld lens. All patients were examined with indirect ophthalmoscopy, with and without red-free light, and with scleral depression. Fluorescein angiography was performed on most patients. Tissue removed from three eyes during the course of vitrectomy was examined histopathologically.

Cytogenetic studies were performed on 10 patients affected with FEVR. Peripheral blood lymphocytes were obtained by venipuncture into heparinized vacutainer, which were centrifuged at 225*g* for 10 minutes to sediment out the white cells as a distinct layer: the buffy coat. The white cells were collected and placed in 10 mL of tissue culture medium, and stimulated to divide by the addition of a mitogenic agent, phytohemagglutinin. The culture was incubated for 72 hours until the cells were multiplying rapidly. A very dilute solution of colchicine (0.2 mL of 10 μg/mL Colcemid) was added to prevent completion of cell division by inhibiting spindle formation and delaying the separation of centromeres. As a result, cells arrested in metaphase accumulated in the culture. To obtain higher resolution, the standard culture conditions were modified by adding actinomycin-D to the final period of culture (40 minutes before harvesting). This allows analysis of the chromosomes at an earlier stage of cell division in order to gain additional information from more elongated chromosomes, which permit high-resolution banding. The cells were pelleted from the medium and washed and incubated in a hypotonic solution (0.075M KCI) for 10 minutes to cause swelling and lysis of cells and release of the chromosomes while keeping the centromeres intact. After centrifuging the cell suspension, cold, freshly made

fixative (3 parts methanol to 1 part glacial acetic acid) was added to the cell pellet for resuspension and the chromosomes were spread on slides. The chromosomes fixed on the slides underwent standard trypsin treatment to denature the chromosomal proteins and then were stained with the Giemsa stain. Each chromosome pair was stained in the characteristic pattern of light and dark bands (G bands) and analyzed under the microscope for karyotyping. Karyotypes were prepared at the 550-band level. Particular attention was paid to chromosome 11, and partial karyotypes of chromosome 11 were prepared at the 650- to 850-band level. Twenty cells were studied for each sample, and three were karyotyped.

RESULTS

CLINICAL FINDINGS

Initial Severity of Retinopathy

On initial examination, in 12 (31%) of the 39 patients the severity of FEVR was mild in both eyes. These patients had no symptoms. Eleven were diagnosed by ocular examination after FEVR was detected in a family member, and one was diagnosed on routine ophthalmic examination. In addition to these 12 patients (24 eyes), 10 patients had unilateral mild FEVR. So, 34 (44%) of 78 eyes were mildly affected. They all had mild straightening of and increased branching of temporal retinal vessels (Fig 1A). All eyes had avascularity of the peripheral retina (Figs 1B and 2). Several eyes had peripheral arteriovenous anastomoses (Figs 1B and 2). Four had mild macular ectopia.

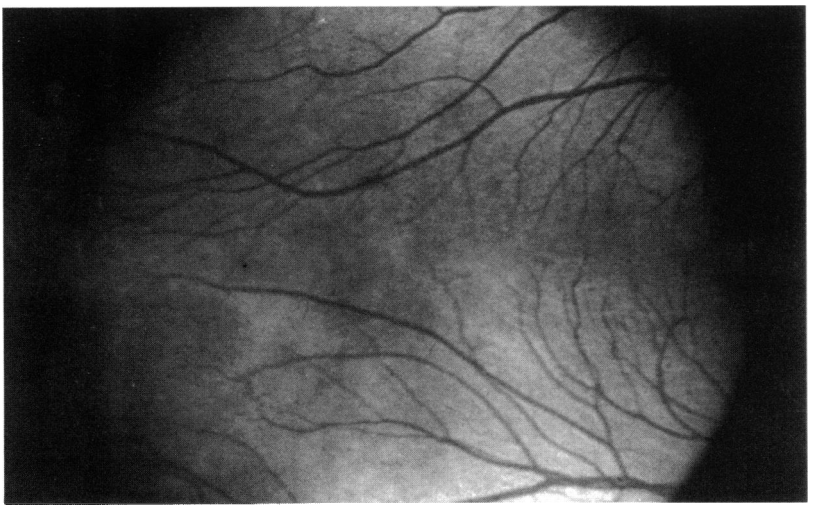

FIGURE 1A

Right eye of asymptomatic patient with FEVR has straightening of vessels in near temporal periphery with increased branching.

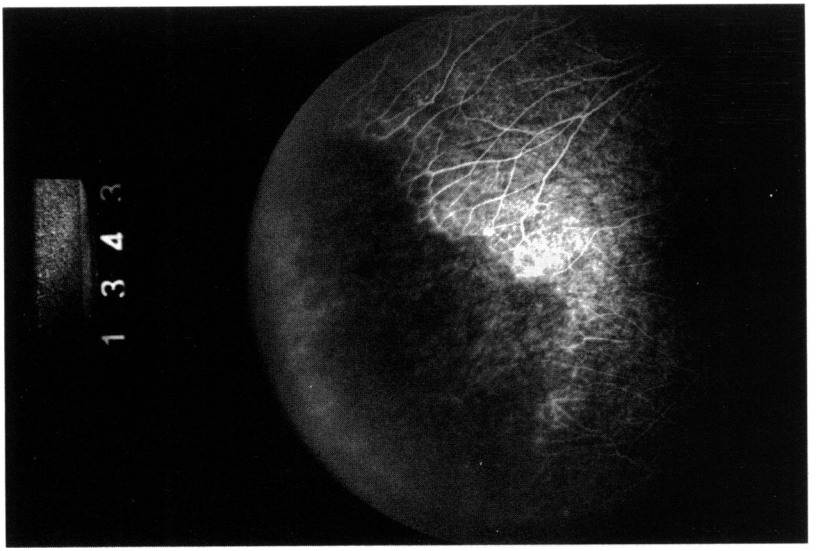

FIGURE 1B

Fluorescein angiography demonstrates V-shaped configuration of capillaries at edge of avascular zone. There are also some small arteriovenous anastomoses.

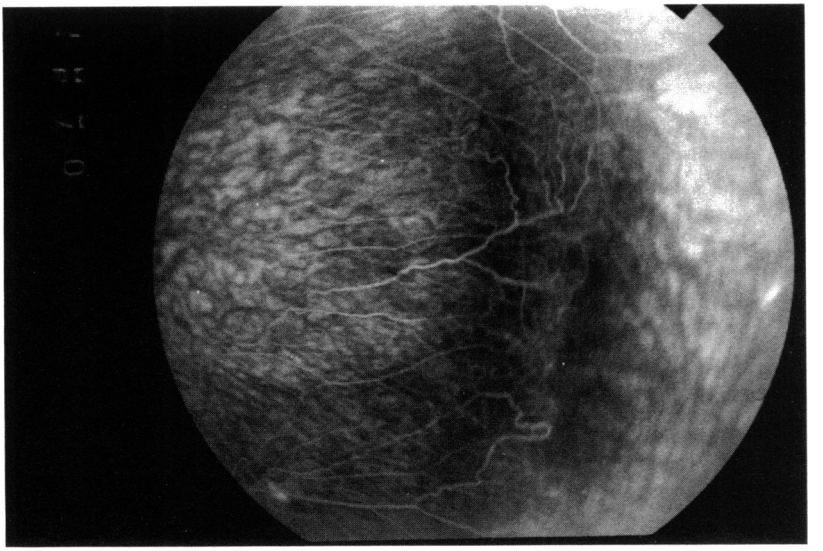

FIGURE 2

Fluorescein angiography demonstrates prominent arteriovenous anastomoses at border of avascular zone in left eye of man whose daughter was legally blind from FEVR.

Twenty-seven of the 39 patients had moderate to severe FEVR in at least one eye with one or more of the following findings (Table 1): Ten eyes (13%) had a total retinal detachment; 20 (26%) had a falciform fold; 12 (15%) had a small peripheral retinal detachment; 14 (17%) had peripheral neovascularization; and 17 (22%) had subretinal or intraretinal lipid exudation.

TABLE I: FINDINGS IN 78 EYES OF 39 PATIENTS WITH FEVR

FINDING	NO. (%)
Avascular zone only	34 (44%)
Total retinal detachment	10 (13%)
Small peripheral retinal detachment	12 (15%)
Falciform fold	20 (26%)
Peripheral Neovascularization	14 (18%)
Subretinal or intraretinal lipid exudation	17 (22%)

Age at Onset of Symptoms

The onset of signs or symptoms was between birth and 12 months in 15 patients (41%), between 1 year and 2.92 years in 2 patients (5%), between 3 and 6 years in 6 patients (16%), and between 15 and 22 years of age in 4 patients (11%). No patient had onset of symptoms between the ages of 7 and 15 years or after 23 years.

The visual outcome was strongly influenced by age at onset of signs or symptoms, the rate of deterioration being most rapid in the youngest patients (Table 2). Of the 17 patients who had the onset before their third birthday, 14 had 3 or more years of follow-up. In their 28 eyes, the final visual acuity was no light perception in 10, light perception in 7, counting fingers in 7, 20/400 in 2, 20/200 in 1, 20/100 in 1, and fixes and follows (with apparent good vision) in 2.

In the 8 eyes of 4 patients who had the onset of symptoms between the ages of 3 and 6 years and who had 3 or more years of follow-up, the final visual acuity was counting fingers in 2, 20/200 in 2, and 20/20 to 20/50 in 4. Retinal involvement was asymmetric in all patients. All four had acuity of 20/40 or better in one eye.

TABLE II: FINAL VISUAL ACUITY OF 46 EYES WITH 3 OR MORE YEARS OF FOLLOW-UP

	AGE AT ONSET OF SIGNS OR SYMPTOMS		
VISUAL ACUITY	BIRTH TO 3 YR	3.08 TO 6 YR	15 TO 22 YR
20/20 TO 20/50		4	5
20/100 TO 20/200	2	2	
20/400 TO CF	7	2	1
HM TO LP	7		2
NLP	10		
F&F	2		

CF, counting fingers; HM, hand movements; LP, light perception; NLP, no light perception; F&F, fixes and follows.

Preservation of good visual acuity into the teens and later was no guarantee that deterioration would not occur. In fact, the final visual acuities of the patients in this group were similar to those of the patients whose age at the onset of signs or symptoms was from 3 to 6 years. In the 8 eyes of 4 patients who were asymptomatic with good visual acuity until 15 years of age, the final visual acuity was light perception in 1, hand movements in 1, counting fingers in 1, and from 20/20 to 20/50 in 5. All 4 patients in this group had asymmetric retinal involvement with acuity of 20/40 or better in one eye.

Rapid Deterioration in Eyes with Neovascularization

Neovascularization of the retina was found to be a grave prognostic sign. It was present in 11 eyes of 9 patients who had at least 3 years of follow-up. Despite treatment with laser, cryotherapy, or vitreoretinal surgery, 7 of the 11 eyes (63%) had a final visual acuity of counting fingers or less. To illustrate how, despite intervention, eyes with neovascularization may deteriorate, the histories of four patients are discussed here. A fifth case (case 11) is discussed later.

Case 1: In this boy, FEVR was diagnosed at the age of 2 months. Both eyes had a wide, 360° peripheral avascular zone, falciform fold, and subretinal

lipid exudation. The left eye showed neovascularization inferotemporally and superonasally (Fig 3). The neovascularization in both eyes was treated directly with cryotherapy but did not respond to three separate treatment sessions over the next 2 months. Two months after the last cryotherapy he had a large nonrhegmatogenous retinal detachment for which the patient underwent a pars plana lensectomy and vitrectomy and additional laser therapy. Nevertheless, the retina remained totally detached and was considered inoperable.

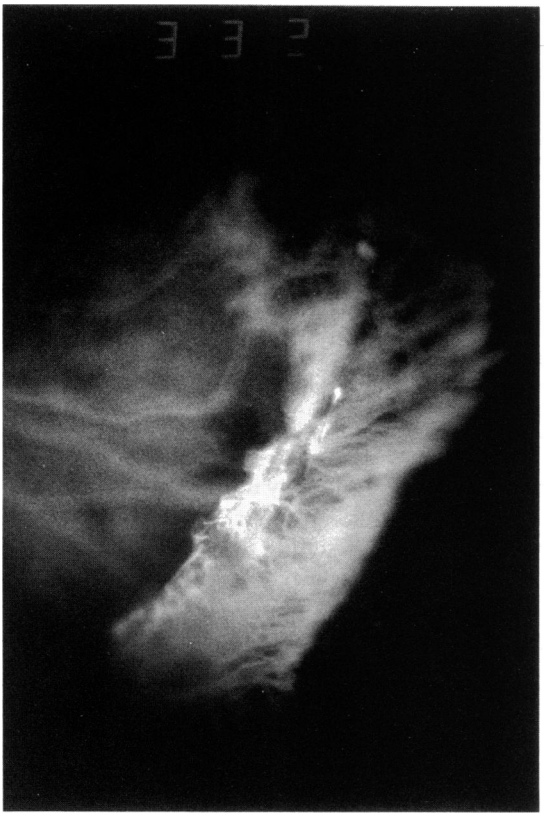

FIGURE 3
Fluorescein angiography demonstrates severe extraretinal neovascularization at junction of vascular and avascular retina in left eye of 3-month-old patient with FEVR.

Case 2: At 13 months of age, this girl was noted to have poor visual acuity in both eyes. On examination under anesthesia, the right eye showed neovascularization and a small vitreous hemorrhage at the edge of the temporal peripheral avascular zone. In the left eye the retina was severely

dragged temporally in a large falciform fold. Two months later the right eye had temporal retinal dragging with a few elevated tufts of neovascularization and some inferotemporal subretinal lipid exudation. The patient was treated with cryotherapy. Two months later she had additional cryotherapy for two new areas of neovascularization. By the age of 8 years, although the neovascularization in the right eye had regressed, the retinal dragging had progressed, a falciform fold had developed, and her visual acuity was counting fingers in both eyes.

Three months later the right eye developed a total rhegmatogenous retinal detachment with proliferative vitreoretinopathy. She underwent a pars plana vitrectomy and lensectomy with a scleral buckling procedure. A retinal break was found just posterior to a cryotherapy scar in the 10-o'clock position. The most remarkable finding at surgery was a thickened sheet of posterior hyaloid similar to that which has been described after treatment of ROP with cryotherapy.[35] Despite this, her retina was reattached; 2 years later the retinas remained unchanged, but her visual acuity was only counting fingers in each eye.

Case 3: At the age of 6 weeks, this boy was noted to have "wandering eyes" and failure to fix or follow. At 3 months of age, on examination under anesthesia, he was found to have a large peripheral avascular zone in both eyes. The retinas were flat, but there was moderate dragging of the vessels and optic disc (Fig 4A). Within 6 weeks, he developed neovascularization in both eyes and increased temporal dragging (Fig 4B).

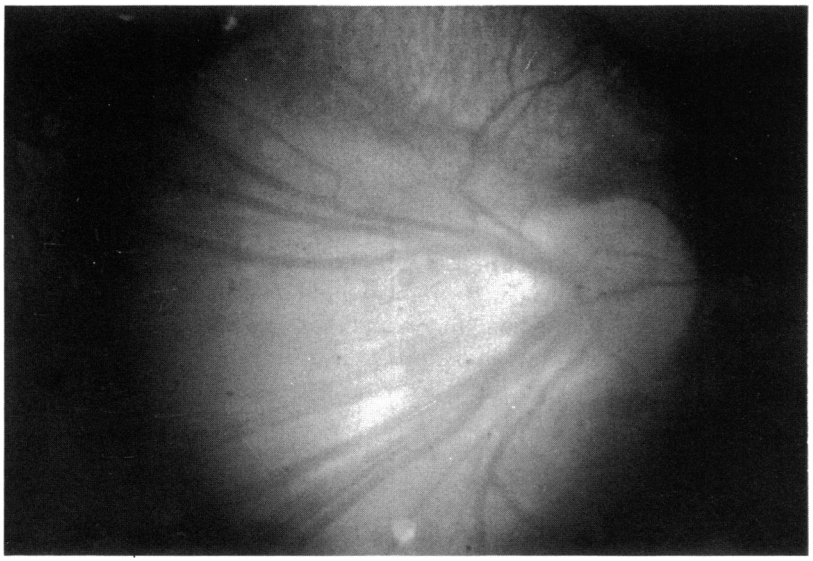

FIGURE 4A

Optic disc in right eye of 5-month-old patient with FEVR is dragged temporally.

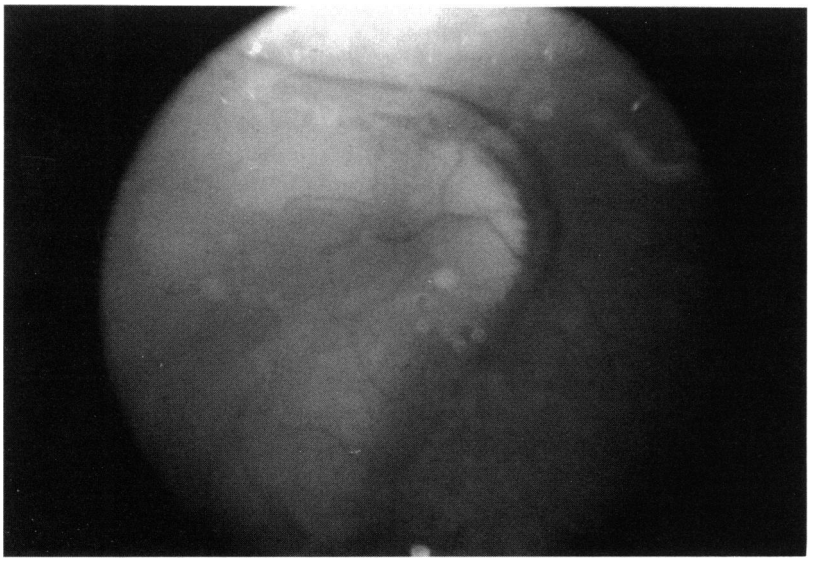

FIGURE 4B
Six weeks later, there is considerably more dragging and temporal nonrhegmatogenous retinal detachment.

The left eye, despite cryotherapy given on two occasions, developed a total inoperable nonrhegmatogenous retinal detachment. The right eye was treated with cryotherapy twice, then developed a rhegmatogenous retinal detachment with a break just posterior to an area of cryotherapy. A vitrectomy failed to reattach the retina and was followed by another vitrectomy combined with a scleral buckling procedure. The retina was reattached but had a residual macular fold. It remained stable for 18 months, after which he was lost to follow-up.

Case 4: An 18-year-old woman, who had had poor vision since childhood, experienced the recent onset of decreasing vision in her right eye. Her visual acuity was 20/200 in the right eye and 20/400 in the left. The left eye had a falciform fold. The right eye had temporal dragging of the retina and optic disc (Fig 5A), a small peripheral nonrhegmatogenous retinal detachment with subretinal lipid exudation (Fig 5B), and peripheral neovascularization (Fig 5, C and D). The right eye was treated with cryotherapy. One month later, the retinal detachment progressed, and she underwent a pars plana vitrectomy, which failed to reattach the retina.

Good Results Despite Neovascularization

Although in most cases neovascularization portended a poor visual outcome, the histories of four eyes will illustrate that the prognosis is not uniformly poor. In the first (case 5), the neovascularization spontaneously regressed.

At the age of 6 years, this girl had an area of neovascularization smaller than 1 disc diameter and slight macular ectopia. The neovascularization was not treated. The vessels gradually became fibrotic, and the macular findings remained unchanged. Fourteen years later, she maintained a visual acuity of 20/50.

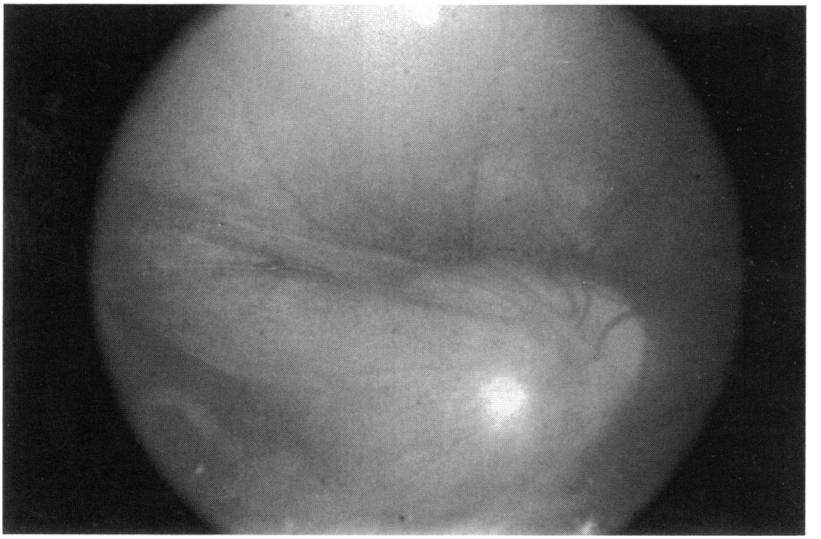

FIGURE 5A
Left eye of 18-year-old woman with FEVR shows severe dragging of optic disc.

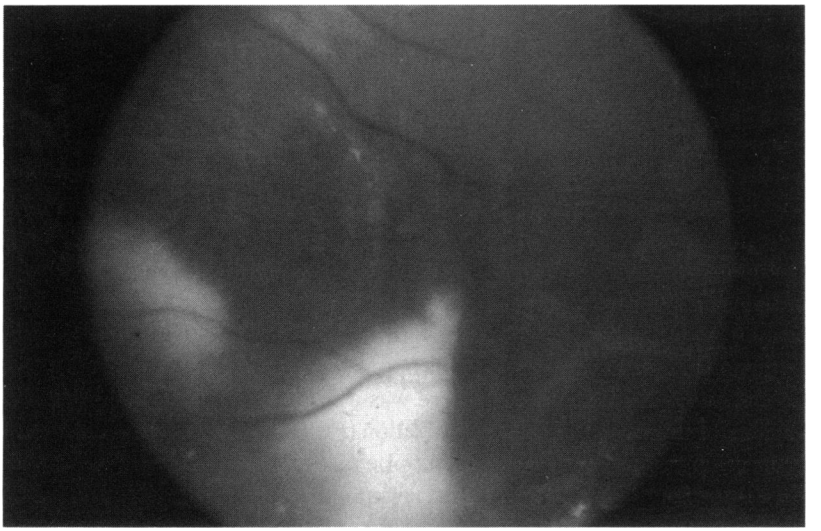

FIGURE 5B
Further peripherally, there is nonrhegmatogenous retinal detachment with subretinal lipid exudation.

FIGURE 5C

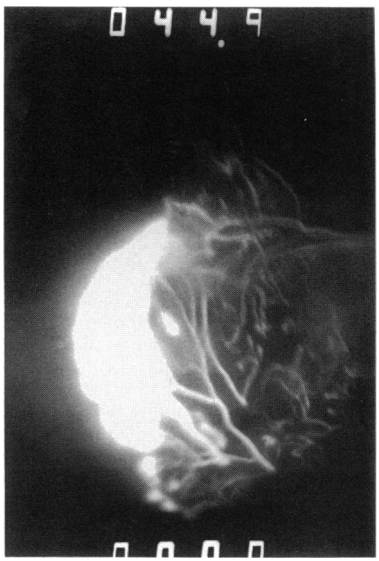

FIGURE 5D

(5C) Fluorescein angiography demonstrates severe extraretinal neovascularization at junction of vascular and avascular retina. (5D) In late phase of angiogram there is severe leakage.

The next three cases had a good response to cryotherapy or laser photocoagulation.

Case 6: At the age of 1 month, this girl was examined because her brother had FEVR with bilateral total retinal detachments. The left eye had peripheral neovascularization and subretinal and intraretinal exudation with retinal dragging and a traction retinal detachment. The avascular zone and neovascularization were treated with cryotherapy. By 6 months later, the exudation had completely resolved. Three years after the treatment, both eyes remained stable with the ability to fix and follow.

Case 7: A woman had laser treatment to the right eye at the age of 18 years. She had good regression of the neovascularization and maintained 20/25 vision for 23 years. (Her left eye is discussed under "Adult FEVR.")

Case 8: A 6-month-old boy presented with peripheral retinal neovascularization and a total nonrhegmatogenous retinal detachment in the right eye. In the left eye there was a wide peripheral avascular zone with a few small tufts of neovascularization (Fig 6A). At the age of 12 months, the left eye had dragging of the left optic disc and fovea (Fig 6, B and C), a peripheral nonrhegmatogenous retinal detachment, and increasing neovascularization (Fig 6, D and E). After treatment with cryotherapy on two occasions, the neovascularization and retinal detachment regressed, but a macular fold remained. Six years later the retina remained flat and the visual acuity was 20/200.

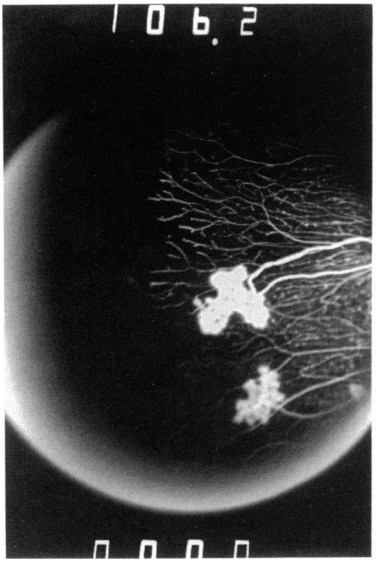

FIGURE 6A

Fluorescein angiography demonstrates two small tufts of extraretinal neovascularization in temporal periphery of 6-month-old boy with FEVR. Note that in this case, there is a brushlike border, but there are no arteriovenous anastomoses.

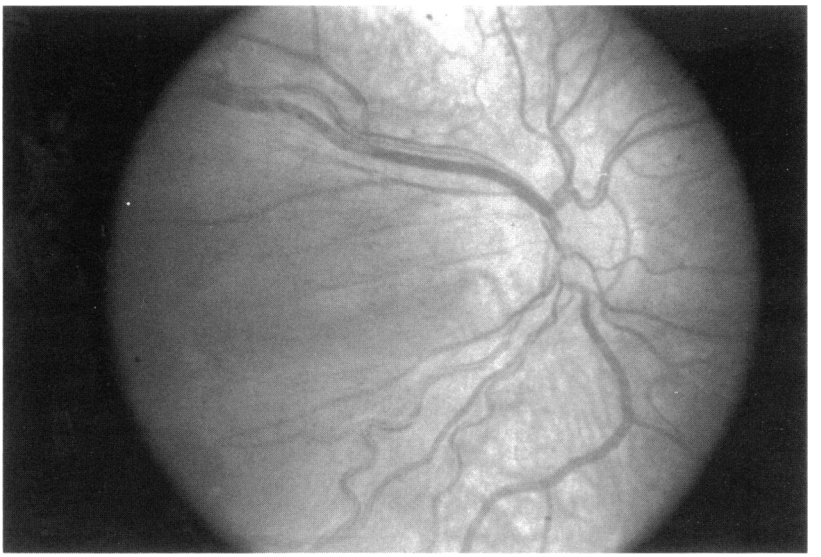

FIGURE 6B

Six months later, macula is dragged temporally and vessels on optic disc are dragged to its temporal side

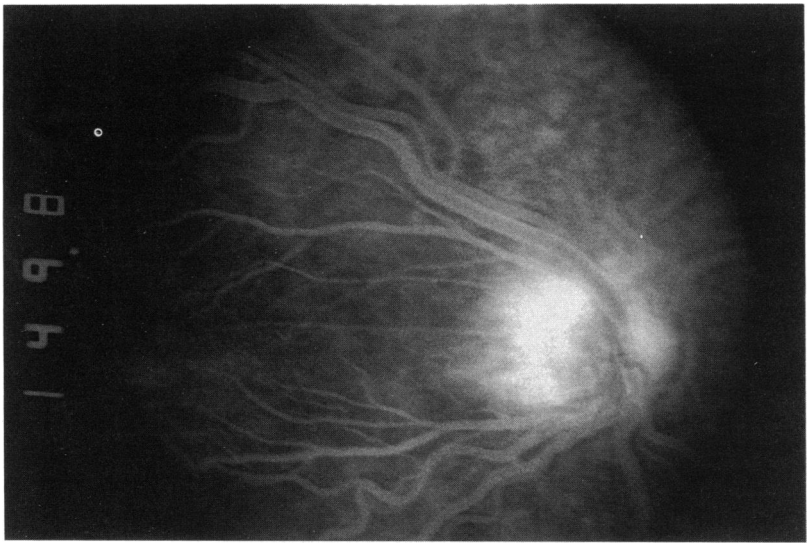

FIGURE 6C
Fluorescein angiography demonstrates leakage from optic disc.

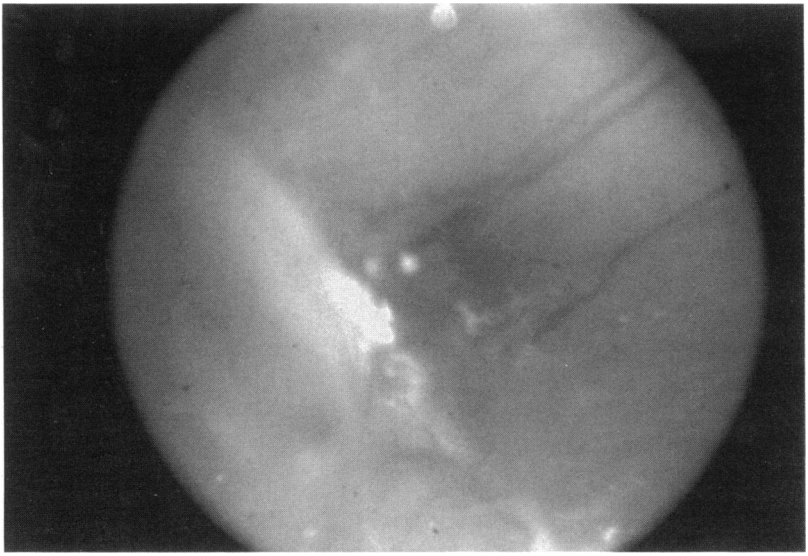

FIGURE 6D
Neovascularization in temporal periphery has dramatically increased in size.

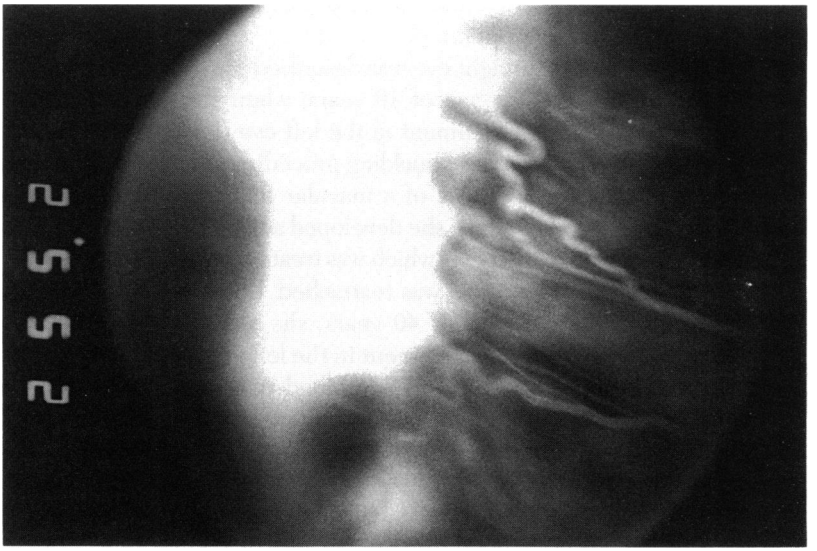

FIGURE 6E
Fluorescein angiography demonstrates severe leakage from neovascularization.

Deterioration Without Neovascularization
Eyes both with and without neovascularization deteriorated. Eleven eyes of 9 patients progressed to retinal detachment involving at least one quarter of the retina and including the macula. Five of the 11 eyes had no neovascularization but still progressed to a significant retinal detachment. This is illustrated by the following case.

Case 9: At the age of 2 years, a boy whose brother had FEVR was noted to have right esotropia. Three months later, examination under anesthesia revealed a wide peripheral avascular zone in the right eye and a shallow temporal nonrhegmatogenous retinal detachment involving the macula. The patient underwent a pars plana lensectomy and vitrectomy with an encircling scleral buckling procedure. The retina was flattened for 6 months, at which time it redetached because of severe proliferative vitreoretinopathy. Despite a second vitrectomy, the retina remained totally detached.

At the time of the original examination under anesthesia, the left eye also had a wide peripheral avascular zone, but the retina was flat. One month later, it had a temporal retinal detachment with macular involvement. A pars plana vitrectomy with lensectomy failed to repair the retina.

Adult FEVR
Of the 37 patients in the database, four (11%) were asymptomatic until late adolescence or early adulthood. Even though infants had the poorest prog-

nosis, the adult patients also suffered significant visual loss. The following case histories illustrate this point.

Case 7 (left eye): (The right eye was described previously.) The patient was asymptomatic until the age of 18 years, when she presented with a rhegmatogenous retinal detachment in the left eye (Fig 7, A and B). The retina was repaired with a scleral buckling procedure, but her vision did not improve beyond 20/400 because of a macular fold (Fig 7C). Seventeen years later, at the age of 35 years, she developed a large nonrhegmatogenous retinal detachment in the left eye, which was treated by revision of the scleral buckling procedure. The retina was reattached, but the vision dropped to counting fingers. At the age of 40 years, she again developed a large nonrhegmatogenous retinal detachment in the left eye and a posterior subcapsular cataract. She underwent a combined pars plana vitrectomy and lensectomy with placement of a posterior chamber lens. The macula was flattened but dragged temporally (Fig 7D), and her vision remained at counting fingers.

The retina in the right eye was stabilized by the initial laser therapy. At the age of 41, its vision dropped to 20/70 because of a posterior subcapsular cataract. She underwent a successful extracapsular cataract extraction with implantation of a posterior chamber lens. Following surgery, the visual acuity improved to 20/25. The retina remained stable.

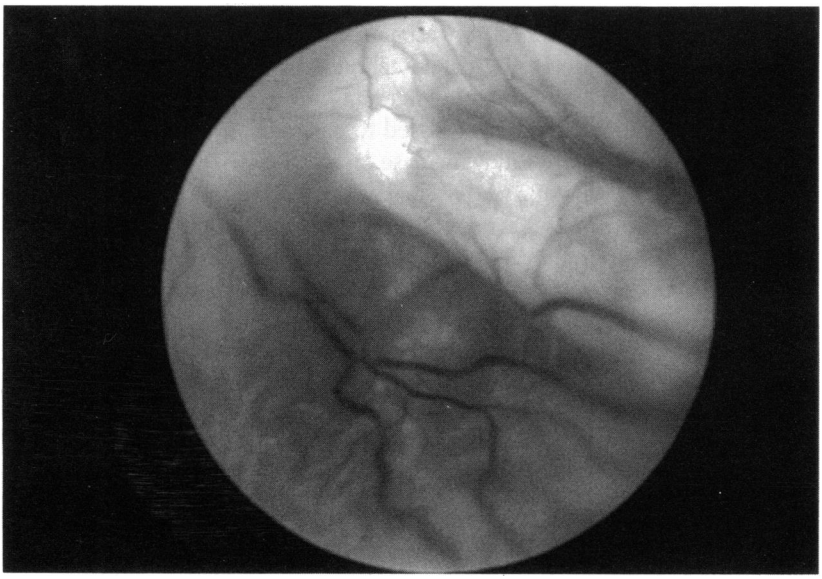

FIGURE 7A

Posterior pole of left eye of 18-year-old patient with rhegmatogenous retinal detachment. Note lipid exudate in macula.

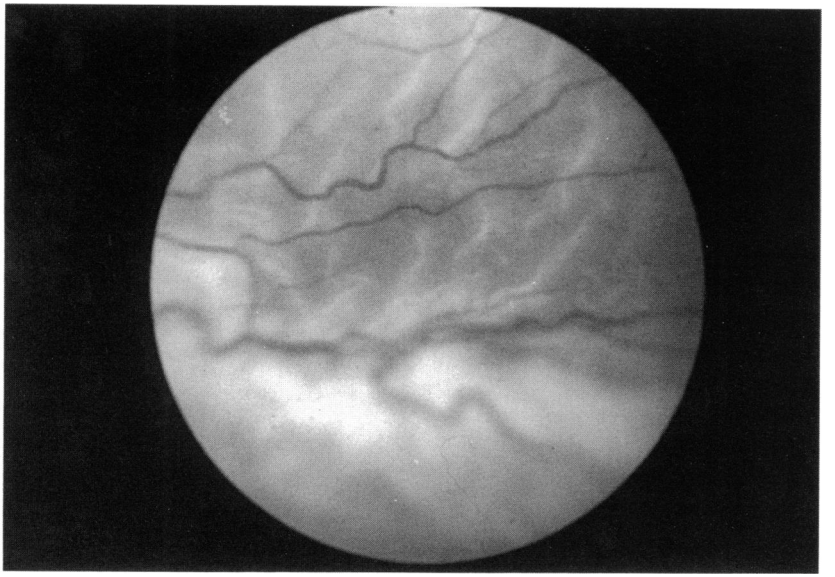

FIGURE 7B
Temporal periphery shows typical corrugated appearance of rhegmatogenous retinal detachment.

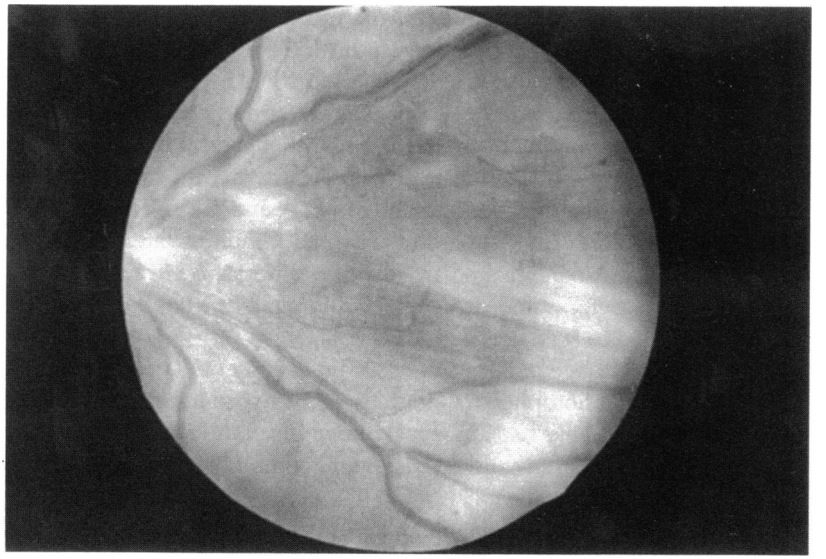

FIGURE 7C
Six months after repair of retinal detachment, macula is flat, but visual acuity did not improve beyond 20/400 because of macular fold.

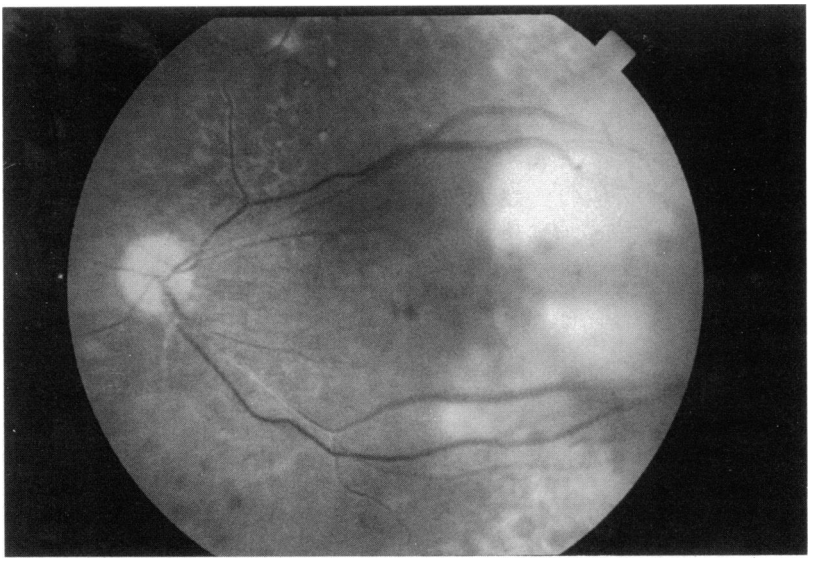

FIGURE 7D
Seventeen years later, after scleral buckling procedure and vitrectomy, macula is flat but visual acuity is counting fingers.

Case 10: This man, whose father was found to have mild, asymptomatic FEVR, had a rapid decrease in vision in his left eye at the age of 22 years. His visual acuity was 20/20 in the right eye and 20/60 in the left. In the right eye the findings were limited to a peripheral avascular zone. The left eye had a temporal peripheral avascular zone with collateral blood vessel formation and a temporal traction retinal detachment with dragging of the macula and subretinal lipid exudation (Fig 8, A and B). He underwent a vitrectomy at another institution and returned 2 months later with a total retinal detachment complicated by severe proliferative vitreoretinopathy. A pars plana lensectomy and vitrectomy with membrane peeling and a large retinotomy failed to reattach the retina.

Case 11: At the age of 22 years, this woman presented with a complaint of hazy vision and photophobia in both eyes. Her visual acuity was 20/25 in both eyes. The right eye had abnormal branching of the retinal vessels, with peripheral vessel sheathing and arteriovenous communications. It remained stable for the following 15 years.

The left eye had mild macular ectopia (Fig 9A) and a peripheral nonrhegmatogenous retinal detachment with preretinal neovascularization and subretinal lipid exudation (Fig 9B). The neovascularization was treated with argon laser photocoagulation three times in the next 3 months and finally regressed. Her vision remained 20/30 for 7 years, at which time she

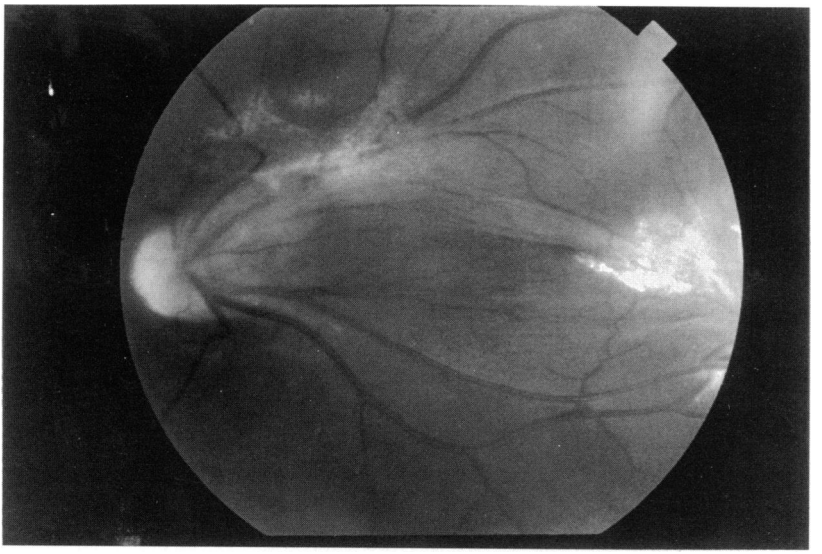

FIGURE 8A
22-year-old man with FEVR. Severe dragging of left macula and macular fold in. Vision is 20/60. Four months earlier, vision was 20/30.

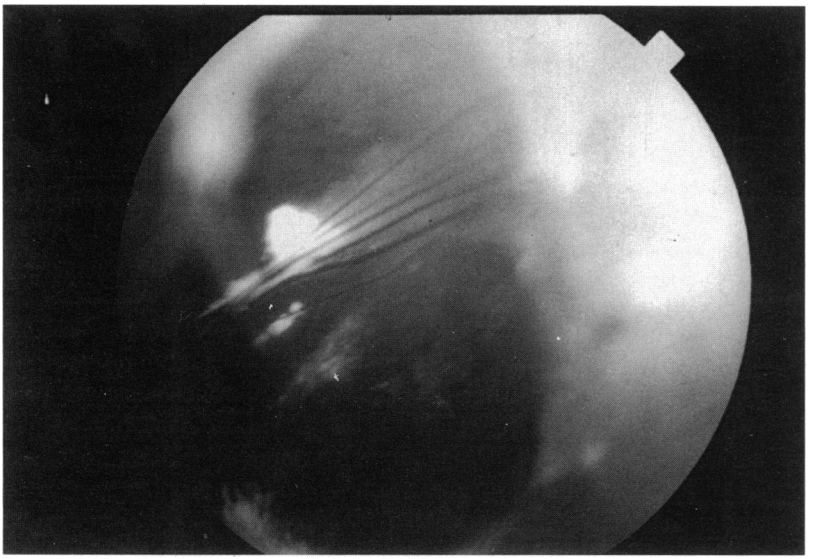

FIGURE 8B
In temporal periphery, there is nonrhegmatogenous retinal detachment with dragging of retinal blood vessels.

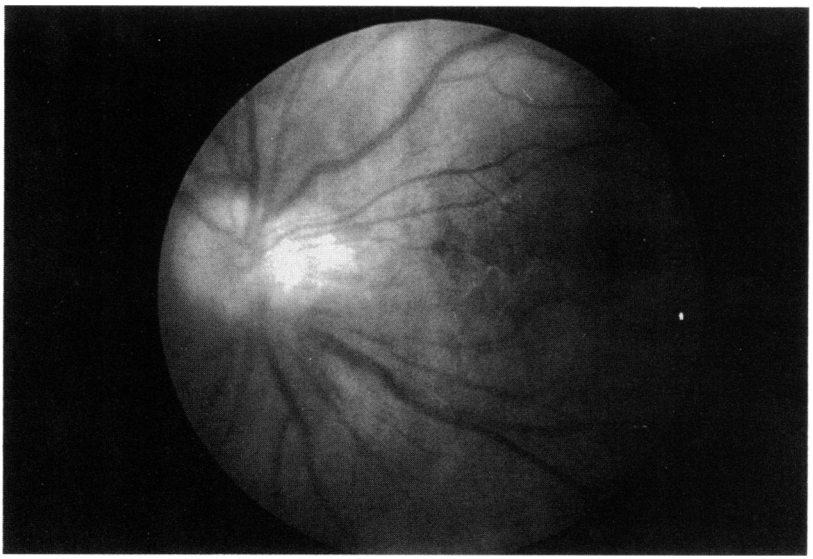

FIGURE 9A
In left eye of a 22-year-old woman with FEVR, macula and optic disc are slightly dragged temporally. Nevertheless, visual acuity is 20/20.

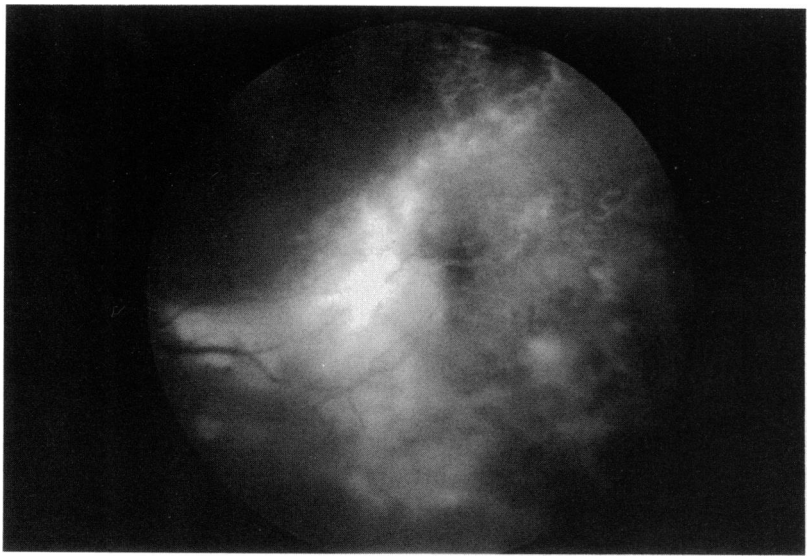

FIGURE 9B
In temporal periphery of same eye, there is subclinical nonrhegmatogenous retinal detachment with subretinal lipid exudate.

developed a vitreous hemorrhage and was treated with additional laser therapy. Despite this treatment, she had recurring vitreous hemorrhages over the subsequent years. Six years later, at the age of 35, she underwent a pars plana vitrectomy for a dense vitreous hemorrhage. Her postoperative visual acuity was counting fingers. Two years later, at the age of 37, because of increasing macular traction with exudation in the posterior pole, she underwent an extracapsular cataract extraction with placement of a posterior lens combined with a pars plana vitrectomy. The retina was flattened, but her visual acuity remained at counting fingers at 18 months' follow-up.

Case 12: At 15 years of age, this boy complained of decreased vision in the left eye. Visual acuity was 20/25 in the right eye and 20/50 in the left. The right eye had mild FEVR with a zone of peripheral avascularity. The left had mild macular dragging. Eight years later, the findings had not changed.

Late Retinal Detachment

Retinal detachment can occur years after the eye appears to be stable (Table 3). Cases 4, 7, and 11 developed a nonrhegmatogenous retinal detachment 17, 17, and 15 years, respectively, after apparent stabilization. Case 2 developed a rhegmatogenous retinal detachment 6 years after cryotherapy. Case 13 developed a rhegmatogenous retinal detachment 8 years after development of a falciform fold. In case 2 the retinal break was just posterior to a cryotherapy scar. The retinal break may also be in the nasal retina, away from the dragged retina, as is illustrated by the next case.

Case 13: At the age of 4 years, this boy, whose mother and grandfather also had FEVR, presented with decreased vision in the left eye. The right eye had slight macular ectopia with temporal dragging of the retina. The left eye had a falciform fold radiating into the periphery. No treatment was given to either eye. At the age of 12 years, he returned with a visual acuity of 20/40 in the right eye and counting fingers in the left eye. Routine examination revealed a superonasal retinal detachment in the left eye with two flap tears. He underwent an encircling procedure with drainage of subretinal fluid. Thirty-four months later, the retina remained attached and the falciform fold was unchanged (Fig 10). The right eye maintained 20/40 vision, and the retina remained unchanged.

Results of Cryotherapy and Laser Photocoagulation

Nine of the 37 patients (24%) were treated with cryotherapy (Table 4). The results were mixed. One patient was lost to follow-up. In 3 cases, a nonrhegmatogenous retinal detachment and, in 1 case, a rhegmatogenous retinal detachment with macular involvement developed within 1 year. In a fifth case, a rhegmatogenous retinal detachment developed 7 years later, with the causative retinal break being just posterior to a cryotherapy scar. In three cases, the neovascularization regressed.

TABLE III: PATIENTS WITH DELAYED ONSET OF RETINAL DETACHMENT

CASE NO.	AGE AT ONSET OF SYMPTOMS (YR)	TREATMENT* PRIOR TO DETACHMENT	AGE AT TIME OF RETINAL DETACHMENT(YR)	TYPE OF DETACHMENT	FINAL VISUAL ACUITY
2	1.3	YES	7	RRD	CF
4	1	YES	18	NRRD	NLP
7	18	YES	35	NRRD	HM
11	22	YES	35	NRRD	CF
13	4	NO	12	RRD	CF

CF, Counting fingers; HM, Hand movements; NLP, No light perception;
NRRD; Nonrhegmatogenous retinal detachment;
RRD, Rhegmatogenous retinal detachment.
*Treatment with laser photocoagulation, cryotherapy, or scleral buckling.

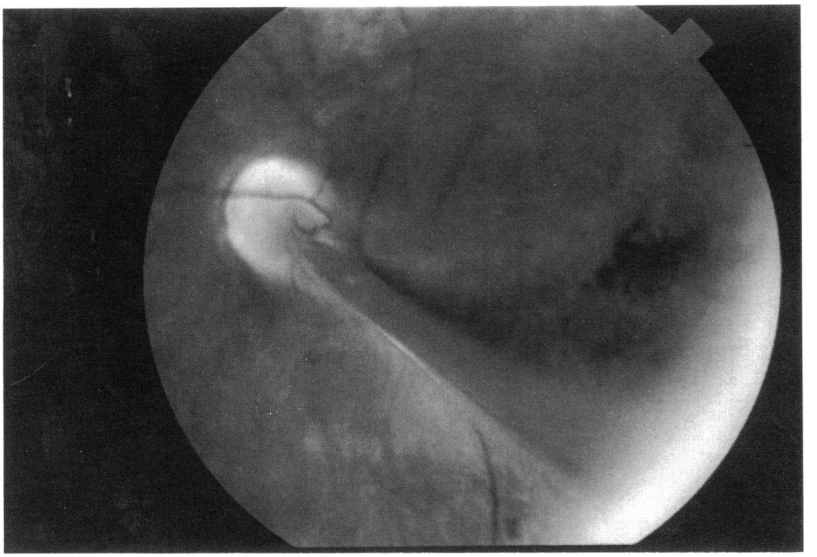

FIGURE 10
Falciform fold through macula of left eye of 12-year-old boy with FEVR. Previously, superonasal rhegmatogenous retinal detachment in same eye had been repaired.

Three patients were treated with laser photocoagulation. In one case, which had also been treated with cryotherapy, a nonrhegmatogenous retinal detachment developed within 3 months. In the second, the patient was stabilized for 7 years, when she developed recurring vitreous hemorrhages. She later developed a nonrhegmatogenous retinal detachment. In the third patient, the neovascularization regressed and the eye remained stable for 13 years.

Results of Retinal Detachment Surgery

We operated on 10 eyes with retinal detachment involving the macula (Table 5). Nine of these developed the detachment after our original examination. One patient (case 3) who developed a detachment was considered inoperable. Some of these patients underwent multiple surgical procedures (Table 4). Six eyes presented with nonrhegmatogenous retinal detachment. The only cure of an eye in which the initial retinal detachment was nonrhegmatogenous was obtained by a vitrectomy in the eye of a 37-year-old woman who had undergone a vitrectomy 2 years earlier for recurring vitreous hemorrhage. In the other 5 patients, despite vitrectomy or vitrectomy combined with a scleral buckling procedure, the retina could not be reattached. Four of the 5 failures were in patients 2 years old or less.

TABLE IV: PATIENTS WITH FEVR WHO UNDERWENT TREATMENT

PATIENT	EYE	AGE	THERAPY		FOLLOW-UP	VISUAL ACUITY	OUTCOME
			TREATMENT	INDICATION			
Case 1	OD	2 Mo	Cryotherapy	Dragged Retina	6 Mo	???	Lost to Follow-up
	OS	2 Mo	Cryotherapy	NVE, Vitreous Hemorrhage	1 Mo	???	NVE Persisted
	OS	3 Mo	Laser	NVE	1 Mo	???	NVE Persisted
	OS	4 Mo	Laser	NVE	2 Mo	???	NVE Persisted
	OS	6 Mo	Vitrectomy	NRRD	2 Mo	?NLP	Total RD
Case 2	OD	13 Mo	Cryotherapy	NVE	3 Mo	???	NVE Persisted
	OD	16 Mo	Cryotherapy	NVE, NRRD	6 Yr	???	NVE Resolved, but 6 yrs later, total RRD
	OD	7.5 Yr	SBP/Vitrectomy	RRD	7 Yr	CF	Retina flat, macular fold
	OS		None	None		CF	Stable, Falciform Fold
Case 3	OD	8 Mo	Cryotherapy	NVE, NRRD	4 Mo	???	No Resolution
	OD	12 Mo	Cryotherapy	NVE, NRRD	4 Mo	???	Developed RRD
	OD	23 Mo	Vitrectomy	RRD	5 Mo	???	Retina was not reattached
	OD	28 Mo	SBP/Vitrectomy	RRD	1.5 Yr	???	Retina flat with residual fold
	OS	5 Mo	Cryotherapy	NVE, NRRD	2 Mo	???	No Resolution
	OS	7 Mo	Cryotherapy	NVE, NRRD	3.25 Yr	???	Total RD
Case 4	OD	18 Yr	Cryotherapy	NVE, NRRD	1 Mo	20/400	NRRD progressed
	OD	18 Yr	Vitrectomy	NRRD	6 Mo	NLP	Total RD
	OS	18 Yr	None		7 Mo	20/200	Insufficient follow-up
Case 5	OD	6 Yr	None	Small tuft of NVE	14 Yr	20/50	NVE atrophied
	OS	6 Yr	Cryotherapy	NRRD	14 Yr	CF	Resolution of NRRD, late cataract
Case 6	OD	1 Mo	None	None	3.16 Yr	F&F	Stable
	OS	1 Mo	Cryotherapy	Neovascularization	3.16 Yr	F&F	Resolution of NVE
Case 7	OD	18 Yr	Laser	NRRD	23 Yr	20/25	Regression of NRRD
	OS	41 Yr	Cataract Surgery	Cataract	6 Mo	20/25	Retina unchanged
	OS	18 Yr	SBP	RRD	17 Yr		Late NRRD
	OS	35 Yr	SBP	NRRD	5 Yr	CF	Late NRRD
	OS	40 Yr	Vitrectomy	NRRD	10 Mo	CF	Retina flat

TABLE IV: PCONTINUED

PATIENT	EYE	AGE	THERAPY		FOLLOW-UP	VISUAL ACUITY	OUTCOME
			TREATMENT	INDICATION			
Case 8	OD	16 Mo	Cryotherapy	NVE, NRRD	5 Yr	20/200	Resolution of NRRD
	OS	16 Mo	None	Inoperable RD	5 Yr	NLP	Total RD
Case 9	OD	2.25 Yr	SBP/Vitrectomy	NRRD	7 Mo	???	Initially retina flat, then NRRD
	OD	2.83 Yr	Vitrectomy	NRRD	15 Yr	NLP	Total RD
	OS	2.33 Yr	Vitrectomy	NRRD	15 Yr	NLP	Total RD
Case 10	OD	22 Yr	None	None	2 Mo	20/20	Mild FEVR, stable
	OS	22 Yr	Vitrectomy	NRRD	2 Mo	LP	Total RD
		22 Yr	SBP/Vitrectomy	RRD	1 Mo	LP	Total inoperable RD
Case 11	OD		None				
	OS	22 Yr	Laser	NVE	1 Mo	20/25	No regression of NVE
	OS	22 Yr	Laser	NVE	1 Mo	20/25	No regression of NVE
	OS	22 Yr	Laser	NVE	7 Yr	20/25	NVE stabilized, later vitreous hemorrhage
	OS	29 Yr	Laser	NVE, Vitreous hemorrhage	6 Yr	20/30	Recurrent vitreous hemorrhages
	OS	35 Yr	Vitrectomy	Vitreous hemorrhage	2 Yr	20/400	Initially clear, then NRRD
	OS	37 Yr	Cataract surgery and vitrectomy	Cataract, NRRD	1.5 Yr	CF	Retina flat
Case 13	OD	4 Yr	None		11 Yr	20/40	Mild FEVR, stable
	OS	12 Yr	SBP	RRD	3 Yr	CF	Retina flat, but falciform fold remains

CF, Counting fingers; F&F, Fixes and follows; NLP, No light perception; NRRD, Nonrhegmatogenous RD; NVE, Neovascularization elsewhere; RD, Retinal detachment; RRD, Rhegmatogenous RD; SBP, Scleral buckling procedure; ???, Patient too young to measure vision.

TABLE V: EYES THAT HAD SURGERY FOR CENTRAL RETINAL DETACHMANT

PATIENT	EYE	AGE	TYPE	SURGERY	RESULT
Case 1	OS	6 Mo	NRRD	Vitrectomy	Failure
Case 2	OD	7.5 Yr	RRD	SBP/Vitrectomy	Success
Case 3	OD	23 Mo	RRD	Vitrectomy	Failure
			RRD	SBP/ Vitrectomy	Success
Case 4	OD	18 Yr	NRRD	Vitrectomy	Failure
Case 7	OS	18 Yr	RRD	SBP	Success
		35 Yr	NRRD	SBP	Success
		40 Yr	NRRD	Vitrectomy	Success
Case 9	OD	2 Yr	NRRD	SBP/Vitrectomy	Failure
				Vitrectomy	Failure
Case 9	OS	2 Yr	NRRD	Vitrectomy	Failure
Case 10	OS	22 Yr	NRRD	Vitrectomy	Failure
				SBP/Vitrectomy	Failure
Case 11	OS	37 Yr	NRRD	Vitrectomy	Success
Case 13	OS	12 Yr	RRD	SBP	Success

NRRD, Nonrhegmatogenous retinal detachment; RRD, Rhegmatogenous retinal detachment; SBP, Scleral buckling procedure.

The other two patients were 18 and 22 years old.

Four patients developed rhegmatogenous retinal detachment. All four were successfully reattached. In a 12-year-old boy (case 13), the retina was reattached with a scleral buckling procedure alone. In a 7-year-old girl (case 2) the retina was reattached with a scleral buckling procedure combined with a vitrectomy. In an 18-year-old woman (case 7) the retina was successfully reattached by a scleral buckling procedure. Seventeen years after this procedure, however, she required a vitrectomy for a nonrhegmatogenous detachment. Five years after the second procedure, she required another vitrectomy for a recurrent nonrhegmatogenous detachment. Finally, a 2-

year-old (case 3) developed a rhegmatogenous retinal detachment 11 months after the second of 2 cryotherapy treatments. A vitrectomy failed to reattach the retina, but it was reattached by another vitrectomy combined with a scleral buckling procedure.

HISTOPATHOLOGY

Histopathologic examination of fluid and ocular tissue fragments obtained during four vitrectomy procedures performed on three patients with FEVR disclosed relatively nonspecific findings consistent with, but not diagnostic of, FEVR. A vitrectomy specimen from a 7-year-old girl contained a fragment of a paucicellular fibrous vitreoretinal membrane. The membrane contained small capillary-caliber vessels, scattered lymphocytes, plasma cells, and macrophages, and a small focus of hemosiderin pigment. Some of the vessels appeared to have undergone involution (Fig 11). A segment of retina also was present (Fig 12). The retinal segment appeared avascular, and its inner half was relatively acellular. Moderate photoreceptor degeneration consistent with retinal detachment also was observed. A vitrectomy specimen obtained from the left eye of a 35-year-old woman (Fig 13) contained several cellular fragments of tissue thought to represent intraocular membranes. These were composed of connective tissue, spindle cells with bland

FIGURE 11

Fragment of vitreoretinal membrane obtained at vitrectomy from 7-year-old girl with FEVR. Fibrous membrane contains capillary-caliber vessels and scattered lymphocytes, plasma cells, and macrophages. Some vessels appear to have undergone involution (hematoxylin-eosin, x100).

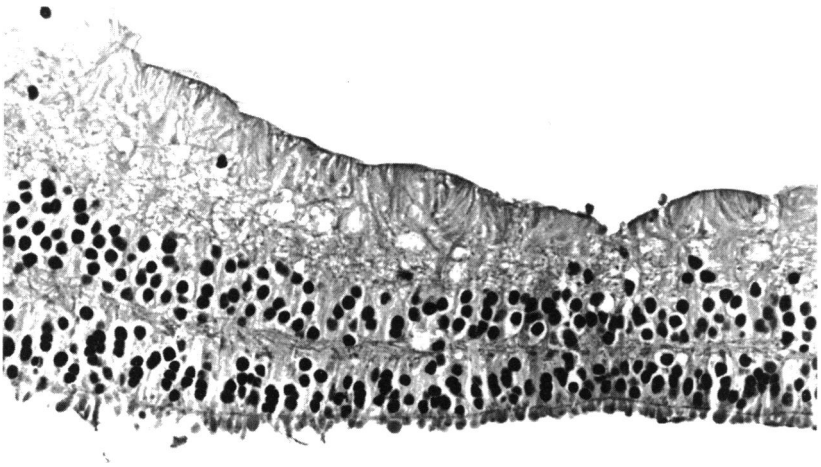

FIGURE 12
Segment of peripheral retina found in vitrectomy specimen from 7-year-old girl with FEVR. Photoreceptor degeneration consistent with chronic retinal detachment is present. No intraretinal vessels are seen. Good preservation of inner nuclear and plexiform layer excludes secondary inner ischemic retinal altorphy (hematoxylin-eosin, x100).

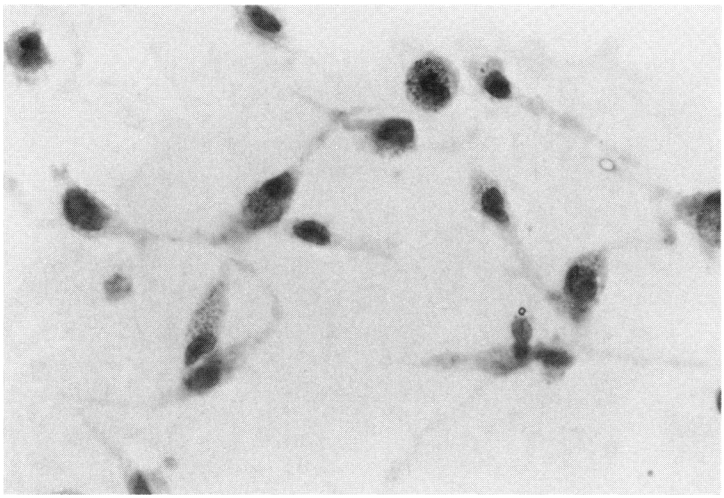

FIGURE 13
Macrophages adhere to surface of vitreous sheet in surgical specimen from 35-year-old woman with FEVR. Most macrophages in this field have assumed spindled or dendritiform configuration. Their cytoplasm contains granules of hemosiderin pigment derived from blood breakdown (hematoxylin-eosin, x250).

oval nuclei, lymphocytes, and macrophages. Many of the macrophages contained abundant amounts of hemosiderin pigment. A few lymphocytes and macrophages that contained blood pigment and had a spindle or dendritic configuration also adhered to sheets and strands of vitreous.

GENETIC STUDIES

The karyotype of 10 patients was studied, with special emphasis on chromosome 11, since the locus for autosomal dominant FEVR has been reported to map on the long arm of chromosome 11. The inheritance of 7 patients was consistent with the autosomal dominant mode of transmission. In the other three the inheritance was sporadic. No evidence for rearrangement, altered size, translocations, or deletions of chromosome 11 or any other chromosome was found (Fig 14). These data do not exclude chromosome 11 or others as the location for some genetic defect related to FEVR, because single base changes and small deletions or insertions may be undetectable by these methods. However, they do rule out involvement of chromosome 11 or others at a gross level.

FINDINGS IN CONDITIONS THAT RESEMBLE FEVR

The database was studied to find similarities and differences between FEVR and conditions that might mimic it: ROP, X-linked retinoschisis, incontinentia pigmenti, Norrie's disease, Coats' disease, pars planitis, Toxocara canis infection, and persistent hyperplastic primary vitreous. The condition that most closely resembles FEVR is ROP.

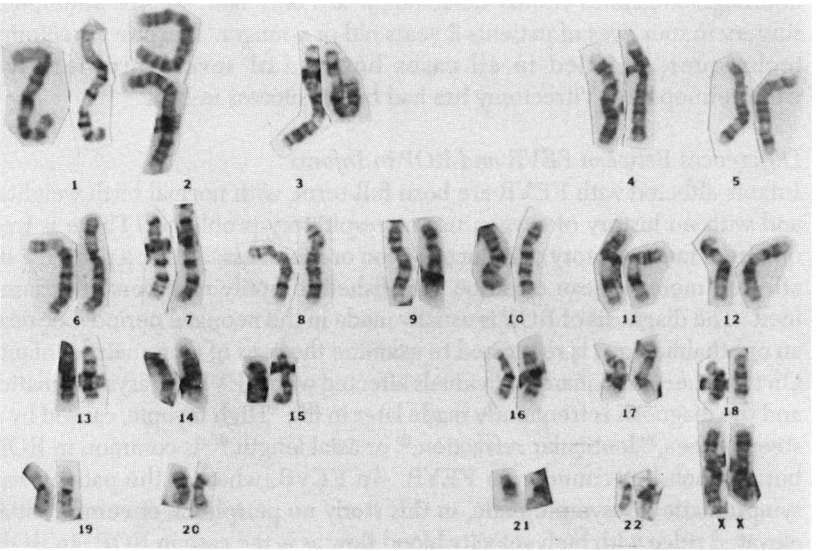

FIGURE 14

Karyotype of patient with FEVR. No gross abnormalities are seen.

Similarities Between FEVR and ROP in Infants

The hallmark of both ROP and FEVR is avascularity of the peripheral retina. ROP causing severe visual loss is most common in infants. The same is true for FEVR. As discussed previously, patients who had the onset of symptoms before their third birthday (Table 1) had a very poor visual outcome. Only 2 of 28 eyes of 14 patients had a final visual acuity of 20/200 or better. Both ROP and FEVR are bilateral, and both may be asymmetric. Of 70 eyes with active ROP that were treated for threshold neovascularization and followed for 12 months, 56 (80%) had symmetric ocular involvement and 14 (20%) had asymmetric involvement. In contrast, of the 17 patients with FEVR who were examined before their third birthday, 7 (41%) had symmetric involvement and 10 (59%) had asymmetric involvement. Thus, in this study, asymmetry was more common in FEVR than symmetry. Cryotherapy has been used to treat both disorders. Because there are so many infants affected with ROP, it was possible to organize a clinical trial to conclusively prove a treatment benefit.[40,41] Similarly, laser treatment has recently been proven to be of benefit in ROP.[42-50] Finally, both may have severe vitreoretinal traction with temporal dragging of the disc and retina, falciform fold, preretinal membranes, and partial or total retinal detachment. Retinal detachment in infants is almost always nonrhegmatogenous but may be rhegmatogenous after cryotherapy.[51] The same is true for FEVR. In the current series, only one child under the age of 6 (case 3) had a rhegmatogenous retinal detachment, and this was after two cryotherapy treatments. In both ROP and FEVR, the results of surgery for nonrhegmatogenous retinal detachment are only fair.[52-54] We attempted surgery in four eyes of patients 2 years old or younger. Despite vitrectomy techniques, it failed in all cases because of severe proliferative vitreoretinopathy. Vitrectomy has had better success in ROP.[55-58]

Differences Between FEVR and ROP in Infants

Infants affected with FEVR are born full-term, with normal birth weights, and with no history of oxygen use or respiratory problems. There is frequently a family history of reduced vision or blindness. If not, a pedigree of affected members can often be established if family members are examined. The diagnosis of ROP is usually made in the neonatal period, because an ophthalmologist is requested to examine the eyes of a premature infant. On the other hand, many individuals affected with FEVR are asymptomatic, and the diagnosis is frequently made later in life. High myopia, caused by a steep cornea,[59] lenticular refraction,[60] or axial length,[61] is common in ROP but is much less common in FEVR. In FEVR, whether the patient was symptomatic or asymptomatic, in this study no peripheral circumferential elevated ridge with high velocity blood flow as is the case in ROP. In ROP, blood vessels may eventually grow into the avascular zone, signaling regression, but in our patients with FEVR, we did not observe this to occur in any

case. Lipid exudation, which was seen in only one eye with ROP, was found in 22% of our patients with FEVR. In patients older than 6 years, FEVR can have nonfibrotic neovascularization, which is a rare occurrence in ROP.

Adult ROP and FEVR

ROP and FEVR are well known as diseases of infants, and it is frequently not recognized that both are lifelong conditions. Patients with regressed ROP can develop late angle-closure glaucoma[62,63] and late rhegmatogenous[64] and traction[65] retinal detachment. In the current series, late complications were seen in 25 (21%) of 120 consecutive patients with adult ROP who were followed for 11 years. Three patients had bilateral complications, so 28 eyes were affected. Nineteen eyes (16%) developed retinal detachment. Average patient age was 30 years (median, 32). Ten eyes of 10 patients had nonrhegmatogenous retinal detachment. Nine eyes of 7 patients had rhegmatogenous retinal detachment. Nine eyes of 8 patients (8%) developed significant cataract. Of these 9, 7 had cataract surgery. Four had intraocular lenses and 3 were aphakic.

The current study shows that the eyes of patients with FEVR also may deteriorate relatively late in life. Seventeen patients were older than 15 years of age. Of their 34 eyes, 4 (12%) had retinal detachment. One of these was rhegmatogenous, and three were nonrhegmatogenous. With regard to the incidence of cataract, of the 34 eyes, 3 had total retinal detachment and dense cataract. Of the remaining 31 eyes, 10 (32%) had a cataract. This was mild to moderate in 7 eyes, but 3 eyes (10%) underwent cataract surgery. All of the operated eyes were visually compromised and tolerated surgery with an intraocular lens well.

X-linked Retinoschisis

Both FEVR and X-linked retinoschisis may present with a dragged retina associated with vitreous hemorrhage.[66-68] Both may have a detached retina, which is amenable to therapy.[68-70] Peripheral neovascularization is very common in FEVR but has also been reported in X-linked retinoschisis.[71-73] We have studied 6 young boys with X-linked retinoschisis and dragged retinas. In all 6, the diagnosis was confirmed by macular changes, family history, electroretinography, and where possible, examination of other family members. In all cases the retina was dragged nasally (Fig 15), unlike the temporal dragging seen in all of our patients with FEVR. Retinal dragging was unilateral in 2 boys and bilateral in 4. Both eyes of 1 patient had recurrent vitreous hemorrhages, and 1 eye had a total retinal detachment. A posterior subcapsular cataract was documented in 1 eye.

Differentiation can also be made by examination of the fellow eye for the characteristic findings of X-linked retinoschisis: spoke-wheel cystoid macular edema, dehiscences of the peripheral nerve fiber layer, and decreased *b* wave on the electroretinogram.[74-75] In both FEVR and X-linked

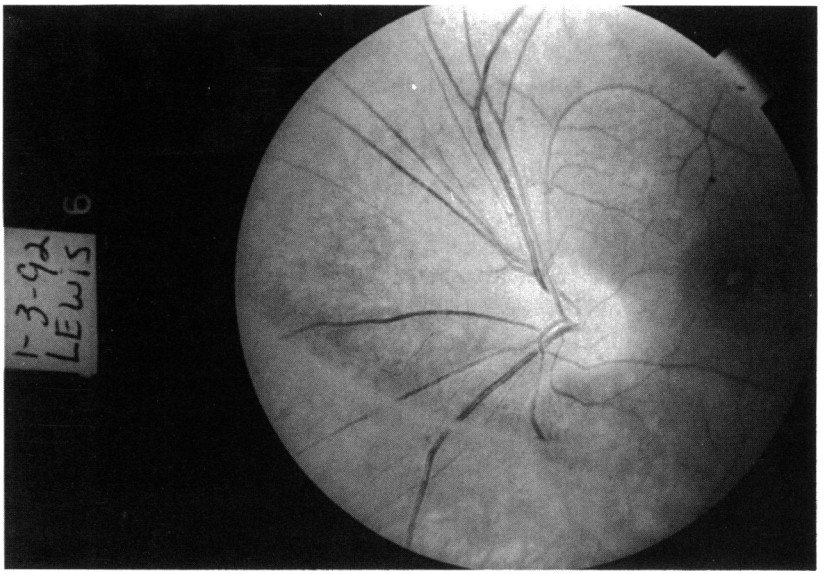

FIGURE 15
Retinal vessles and optic disc are dragged temporally in right eye of boy with X-linked retinoschisis.

retinoschisis a positive family history is often obtained. Although FEVR can be inherited as X-linked or sporadic, the majority of cases are autosomal dominant. Therefore, girls are rarely found with X-linked retinoschisis, but are commonly found with FEVR. In the current series, one maternal grandfather of a 7-year-old boy with X-linked retinoschisis had a decreased *b* wave on electroretinography. His macula no longer had the typical spokelike appearance, but showed only retinal pigment epithelial thinning that simulated dry macular degeneration.

Incontinentia Pigmenti (Bloch-Sulzberger Syndrome)
Incontinentia pigmenti is an X-linked dominant condition that is lethal in males and therefore is seen only in females. Affected patients may have cataract, myopia, nystagmus, cerebral ischemia, cortical blindness, and blue sclera.[76] The diagnosis is made by observation of or a history of the characteristic bullae or red nodules on the skin in the perinatal period. These eruptions later become depigmented. Furthermore, incontinentia pigmenti is associated with central nervous system abnormalities, occasional mental retardation, epilepsy, seizures, and spastic paralysis.

The spectrum of fundus abnormalities in incontinentia pigmenti is wide and may be difficult to differentiate from FEVR on the basis of the ocular

examination alone. It runs the gamut from dilated and tortuous retinal vessels with peripheral retinal nonperfusion to total closed-funnel retinal detachment with severe proliferative vitreoretinopathy. In incontinentia pigmenti as in FEVR, there may be a very rapid deterioration of the retina to total retinal detachment.[77] Foveal hypoplasia has recently been reported.[76] Of 6 patients in the current series with this condition, 3 were infants. One presented with bilateral closed-funnel retinal detachment. Two other girls progressed from a picture of avascular retina resembling FEVR in 1 eye (Fig 16) to total retinal detachment with proliferative vitreoretinopathy within the first 4 months of life. In both of these girls, the fundus in the fellow eye had a normal appearance. The mother and maternal aunt of 1 baby had symmetric avascular zones in the fundus periphery bilaterally but were totally asymptomatic from the ocular standpoint. The maternal aunt had de-

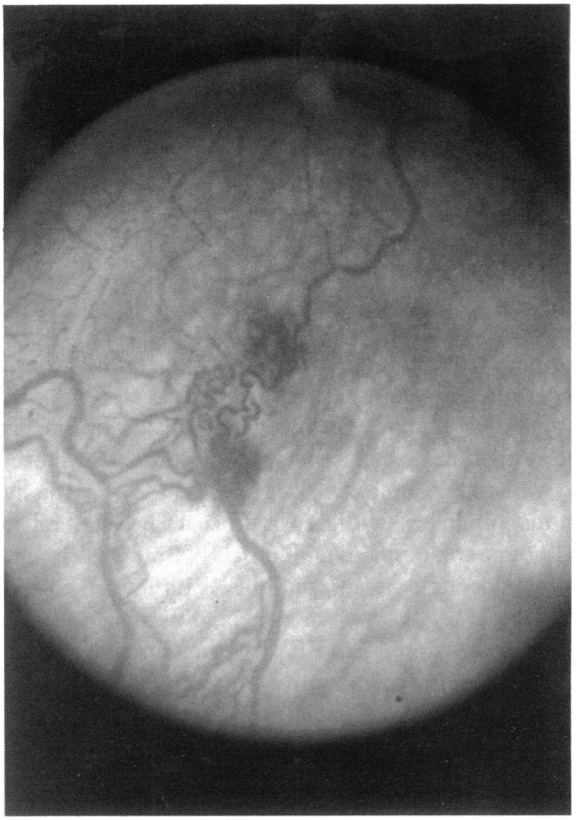

FIGURE 16

Temporal periphery of girl with incontinentia pigmenti shows peripheral avascularity, dilated blood vessels, and arteriovenous anastomoses.

pigmentation of the skin on 1 leg. Neither had previously been diagnosed as having incontinentia pigmenti. The mother of the other little girl who progressed to proliferative vitreoretinopathy in 1 eye had leukokoria of the right eye and angiographically demonstrable avascularity of the peripheral retina in the asymptomatic fellow eye.

Thus, both FEVR and incontinentia pigmenti may be blinding diseases, but they may be totally asymptomatic and diagnosed only after the diagnosis is suggested by examination of a symptomatic female infant. Furthermore, both conditions are asymmetric in approximately one half of affected individuals. Of the 6 patients (12 eyes), 2 infants and 1 mother (50%) showed asymmetry, and symmetric changes were noted in 1 infant, a mother, and a maternal aunt (50%).

Norrie's Disease

As already mentioned, Norrie's disease is inherited as an X-linked recessive trait. Some cases may be allelic with FEVR. Because both conditions may have bilateral retinal folds and peripheral retinal masses, they may be difficult to differentiate. Ocular features of Norrie's disease include microphthalmia and corneal opacification, both of which are uncommon in FEVR. In addition, patients with Norrie's disease may be mentally retarded and deaf. They may also have increased susceptibility to infection, stunted growth, and hypogonadism. No patients with this condition are included in this series.

Coats' Disease

In some eyes with FEVR, subretinal lipid exudation can be so severe that it may resemble Coats' disease. In both, peripheral capillaries may be dilated, giving a coarsened appearance to the capillary bed, and both may have exudative retinal detachment. However, in FEVR, a fibrous preretinal membrane and retinal traction are nearly always present if there is an extensive exudative retinal detachment. Also, Coats' disease is usually unilateral and more common in males, whereas FEVR is always bilateral and in our series was equally common in males and females. Both FEVR and Coats' disease may have telangiectatic vessels, but in FEVR they are much less prominent and rarely have a "light bulb" shape. Neovascularization is rare in Coats' disease but is more common in FEVR. In a follow-up of 42 eyes with Coats' disease, we encountered only one that progressed to retinal neovascularization.

Pars Planitis

Pars planitis may mimic FEVR because it is most common in young patients, is usually bilateral, and can cause a falciform fold, retinal detachment, and peripheral neovascularization. The "snowbank" may be mistaken for lipid exudation, but it is mostly preretinal and is most prominent inferi-

orly. In FEVR, the true lipid exudates are usually located more temporally than inferiorly and are intraretinal or subretinal. In pars planitis, all patients have vitreous cells and many have vitreous "snowballs" and anterior chamber cells as well, whereas in FEVR, signs of uveitis are rare. In cases of FEVR, a positive family history can usually be established, but pars planitis is only rarely familial.

Toxocara Canis

Toxocara canis infection may present in infants as a peripheral granuloma with macular dragging and a falciform fold. Unlike FEVR, however, it is unilateral and there is associated uveitis, a history of exposure to puppies, and vitritis.

Persistent Hyperplastic Primary Vitreous

This condition has two findings that may also be seen in FEVR: total retinal detachment and an occasional prominent retrolental membrane. However, unlike in FEVR, leukokoria is usually present at birth. Also, of 6 patients with this condition seen or operated on since 1989, only 1 has had bilateral involvement. Finally, FEVR is not associated with microphthalmia, nor does it have prominent ciliary processes, a shallow anterior chamber, radial remnants of the tunica vasculosa lentis, or, in early cases, cataract.

DISCUSSION

LONG-TERM PROGNOSIS

This study confirms the hypothesis that the long-term prognosis for patients with FEVR is guarded. Five patients whose condition appeared to be stable deteriorated many years later. Three developed nonrhegmatogenous retinal detachment from 15 to 17 years after their first examination. Two patients developed rhegmatogenous retinal detachment from 6 to 8 years later. Four patients were asymptomatic until they were at least 15 years old and then developed macular dragging or retinal detachment. Three of these 4 had a final visual acuity of counting fingers or worse, and surgery was required in some patients in their late 30s and early 40s. Thus, published surgical success rates with less than 20 years' follow-up may be inaccurate. Further, this series shows that cataract is a late complication in a significant number of patients with FEVR, even if the retina is attached. Although others have reported that cataract is not a prominent feature of FEVR, in this series 32% of patients older than 15 years had clinically significant cataract and 10% required cataract surgery. In all 3, the cataract surgery did not precipitate retinal deterioration.

Patients who had the onset of signs or symptoms before their third birthday fared considerably poorer than older patients. Despite the finding of asymmetry in 59%, even the better eye eventually did poorly. In this age-

group, only 2 of 28 eyes (7%) had visual acuity of 20/200 or better in the better eye. In patients with the onset of symptoms after 3 years of age, 100% had asymmetric involvement and all patients had visual acuity of 20/50 or better in 1 eye.

VALUE OF TREATMENT

Cryotherapy and Laser Photocoagulation

The value of treatment of FEVR has never been established. The current series shows that patients with neovascularization have a poor prognosis, even with cryotherapy or laser photocoagulation. There were 11 eyes of 9 patients with neovascularization who had 3 or more years of follow-up. Seven of these, despite treatment with cryotherapy or laser photocoagulation, had a final vision of counting fingers or worse. This is not to say that all eyes with neovascularization do poorly. One eye had a tiny tuft of neovascularization that regressed spontaneously and remained inactive over a 14-year period of follow-up. Three eyes responded well to treatment.

Retinal Detachment Operations

In the literature, most patients who had a successful surgical result had a scleral buckling procedure,[6,7,16,26,32] and poor results were obtained when vitrectomy was employed. This is true whether the surgery was done for a nonrhegmatogenous or a rhegmatogenous retinal detachment. We operated on 10 eyes with retinal detachment. Six of these presented with nonrhegmatogenous retinal detachment. The only cure of an eye in which the initial retinal detachment was nonrhegmatogenous was obtained by a vitrectomy in the eye of a 37-year-old woman who had undergone a vitrectomy 2 years earlier for recurring vitreous hemorrhage.

Four of the 11 initially had a rhegmatogenous retinal detachment. Two of these were repaired by a scleral buckling procedure alone, but 1 of the 2 (case 7) required a revision of the scleral buckling procedure 17 years later for a nonrhegmatogenous retinal detachment as well as a vitrectomy for recurrent nonrhegmatogenous retinal detachment 5 years after that. The third rhegmatogenous detachment, which occurred in a 7-year-old-girl, was repaired by a vitrectomy combined with a scleral buckling procedure. The fourth was in a 2-year-old. A vitrectomy alone failed, but a reoperation combining a vitrectomy with a scleral buckling procedure was successful.

Others have reported the poor success rate of retinal detachment surgery in children.[12,15,26,32] Of the 3 patients younger than 16 who had successful repair of nonrhegmatogenous retinal detachment, 2 were treated with scleral buckling alone and 1 by vitrectomy.[34] This study confirms their results. Only 4 retinal detachments were repaired in patients younger than 18 years old. The ages of these patients were 2, 7, 12, and 18 years. All had rhegmatogenous retinal detachment. The 18-year-old is classified as a success, but as mentioned previously, she developed a nonrhegmatogenous

detachment 17 years later.

Only 2 of 8 nonrhegmatogenous retinal detachments were successfully repaired, both in patients in their fourth decade of life. Vitrectomy was of benefit in only 4 of 11 eyes it did not help in 7. The main cause of failure was severe proliferative vitreoretinopathy.

SIMILARITIES AND DIFFERENCES BETWEEN FEVR AND ROP

This study shows that FEVR and ROP have several similarities in appearance and outcome. In both, surgery in children with nonrhegmatogenous retinal detachment has a poor prognosis. In both, late vitreous traction can cause a nonrhegmatogenous or rhegmatogenous retinal detachment in the late teens, 20s, or 30s. In both, the late incidence of cataract is higher than previously believed.

The main differences are that in FEVR there is no history of prematurity or of oxygen, there is a positive family history, there is no peripheral ridge in the early stages, there is often a V-shaped avascular zone with a brush border, and there is no late vascularization of the avascular zone. Finally, 22% of patients with FEVR have subretinal or intraretinal lipid exudation, which is a rare occurrence in ROP.

SIMILARITIES AND DIFFERENCES BETWEEN FEVR AND OTHER CONDITIONS

Incontinentia pigmenti and Norrie's disease are the conditions whose ocular findings most closely resemble FEVR. In both, the initial finding is a peripheral avascular zone. Norrie's disease must be distinguished on the basis of a good general physical examination. Incontinentia pigmenti may cause total blindness in infants but, like FEVR, may not progress, so an affected adult may be totally asymptomatic. In such a patient, the diagnosis must be made by a careful dermatologic and neurologic history and physical examination.

GENETIC STUDIES

Other investigators have localized a genetic defect to chromosome 11. In the karyotype studies reported here, no evidence for rearrangement, altered size, translocations, or deletions of chromosome 11 or of any other chromosome was found, ruling out involvement of chromosome 11 or others at a gross level. However, this did not exclude them as the location for some genetic defect related to FEVR, because single base changes and small deletions or insertions may be undetectable by the methods utilized.

SUMMARY

This study has shown that the prognosis for FEVR patients with the onset of symptoms prior to their third birthday is poor. Only 2 of 28 patients in this age-group had a final visual acuity of 20/200 or better. Older patients have

a better prognosis, because they are more likely to have asymmetric retinal deterioration with only one eye deteriorating. Nevertheless, they are still at risk, because FEVR is a lifetime disease. Patients can never be considered to be in a permanently stable status. Five patients whose onset of symptoms was before their 7th birthday developed a macula-involving retinal detachment 6 to 17 years later. One patient whose retina had been apparently successfully reattached suffered a redetachment 17 years later.

Patients who become symptomatic later in life are also at risk. Of the 37 patients in this series, 4 (12%) were asymptomatic until they were older than 15 years. Three of the 4 developed a retinal detachment with a poor visual outcome. Another late complication was cataract, which was found in 32% of those who did not have a total retinal detachment. Of the patients older than 15, 10% required cataract surgery. Of a similar group of patients with ROP, 16% developed a retinal detachment and 8% required cataract surgery.

The presence of neovascularization is a grave prognostic sign, as 63% of eyes with it had a final visual acuity of counting fingers or less. However, vitreous traction can develop in its absence. Of the 11 eyes that progressed to retinal detachment under our observation, 5 had no neovascularization.

The prognosis of progressing FEVR is poor, even with treatment. Despite cryotherapy or laser treatment for neovascularization, 4 of 8 eyes progressed to retinal detachment. The prognosis for repair of rhegmatogenous retinal detachment is better than that of nonrhegmatogenous detachment. All four rhegmatogenous detachments were reattached, whereas only 1 of 7 nonrhegmatogenous detachments was reattached. Review of the literature and the results of this series suggest that the surgeon should consider a scleral buckling procedure alone if a patient develops a retinal detachment. All three scleral buckling procedures without vitrectomy were successful for at least 3 years. On the other hand, 9 of 11 operations in which vitrectomy was used were failures.

No evidence for rearrangement, altered size, translocations, or deletions of chromosome 11 or any other chromosome was found, ruling out involvement of chromosome 11 or others at a gross level, but not excluding them as the location for some genetic defect related to FEVR, because single base changes and small deletions or insertions may be undetectable by the methods utilized.

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