Principles and Practice of Clinical Electrophysiology of Vision

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The Use of Fluorescein Angiography as an Adjunct to Electrophysiological Testing

John Heckenlively

While there are a number of retinal diseases where the electrophysiological test results are distinctive and often highly characteristic, the usual case undergoing evaluation needs to have other parameters assessed in order for a diagnosis to be reached. Typically, the diagnostic information considered includes the age of onset, inheritance pattern, symptoms, and morphological changes as seen on examination or in photographs; these are correlated with the results of electrophysiological and psychophysical testing.

One test that normally might not be thought to be of much value in electrodiagnosis is fluorescein angiography (FA) and fundus photography (FP). However, there are a number of situations where the FA and FP can strongly support or give the correct diagnosis. On occasion, additional information is learned about the disease process that may have clinical importance.

BASIC PRINCIPLES OF FLUORESCEIN ANGIOGRAPHY

Briefly, FA testing is based on the fact that blue light stimulates or excites fluorescein molecules to emit bright green light, which can be recorded selectively by the use of transmission filters on film or by video camera.[2, 18, 19] The fluorescein is normally injected as a bolus in an antecubital vein and reaches the eye through the circulatory system in about 10 seconds. Since the fluorescein dye is blood borne and is a moderately large molecule, it normally does not leave retinal blood vessels because of the endothelial cells' tight junctions. If the vessels are involved in an active inflammatory process, or have lost their tight junctions due to scarring, dye leaks or stains the tissue.

Since choroidal vessels do not have tight junctions, free passage of fluorescein takes place in the choroid, which contributes to the "choroidal flush" seen in the early transit phase of the FA. The confluent nature of the retinal pigment epithelial (RPE) monolayer, which also has tight junctions, prevents leakage of the fluorescein into the subretinal space.

If the RPE is damaged, it may diffusely or focally leak in recognizable patterns, or if the cells are filled with pigmented material, the choroidal flush is blocked and gives what has been termed the "dark choroid effect."[1, 5] Changes in the status of the retinal and choroidal vasculature systems are easily seen with FA. How quickly the fluorescein appears, what layer is affected, whether it is a diffuse slow, active early leak or stain or late stain all give important diagnostic information.

HEREDITARY RETINAL DISEASES WITH DISTINCTIVE FLUORESCEIN ANGIOGRAMS

Choroideremia

The choroideremia pattern is not always obvious on fundus examination, particularly in children or in patients who have more choroidal pigmentation. Visual physiological studies usually demonstrate a rod-cone loss pattern on the electroretinogram (ERG), elevation of the rod thresholds, and often ring

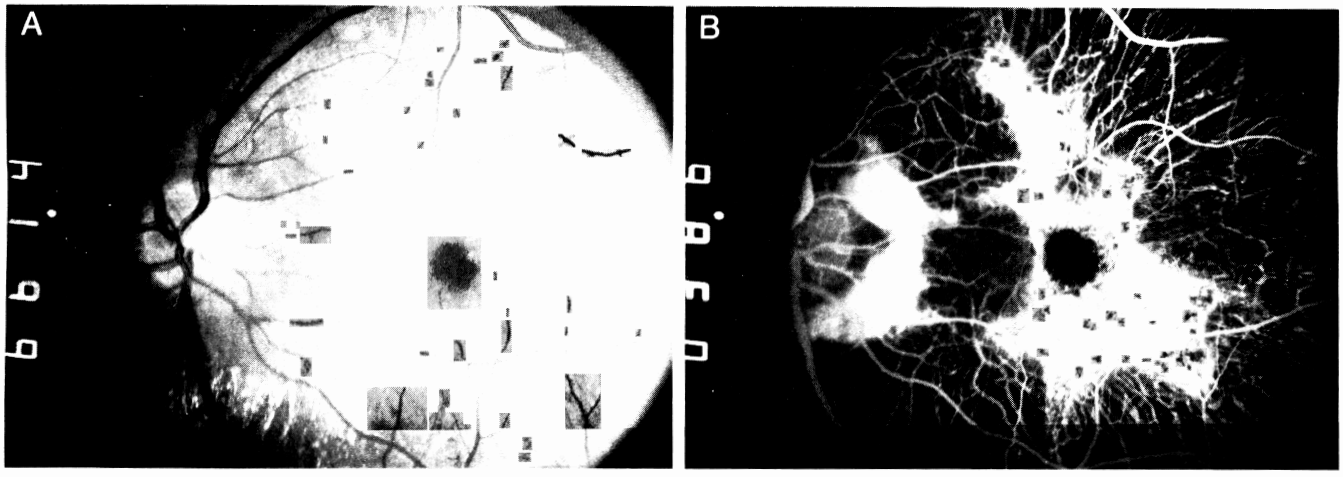

FIG 62–1.
Choroideremia in a 22-year-old Japanese man from an X-linked recessive family pedigree. **A,** a red-free photograph, left eye, demonstrates choroidal pigmentation that almost masks an island of intact *RPE* in the macula. **B,** FA of the same area demonstrates two islands of patent choriocapillaris in the macula and parapapillary area, with loss of choriocapillaris and small choroidal vessels outside the patent areas. The fovea is hypofluorescent, probably from thickened RPE.

scotomas or constricted fields (see Chapter 86).[13, 17] Usually an X-linked recessive inheritance pattern can be established.

The FA in choroideremia shows a distinctive scalloped loss of the choriocapillaris, which is hypofluorescent next to brightly hyperfluorescent patent choriocapillaris (Fig 62–1,A and B). With only the clinical history and ERG results, the diagnosis of X-linked retinitis pigmentosa (RP) might be made, yet this conclusion would miss the more precise diagnosis of choroideremia, which can be made by the examination of the fundus directly and confirmed by FA in cases where choroidal pigmentation masks the choriocapillaris/RPE dropout.

The appearance of lobular loss of RPE and choriocapillaris on FA that is confined primarily to the posterior pole can also be seen in Bietti's crystalline retinal dystrophy (Fig 62–2,A and B) (see Chapter 90). Pericentral RP will have selective loss of RPE and choriocapillaris at the edge of the posterior pole to

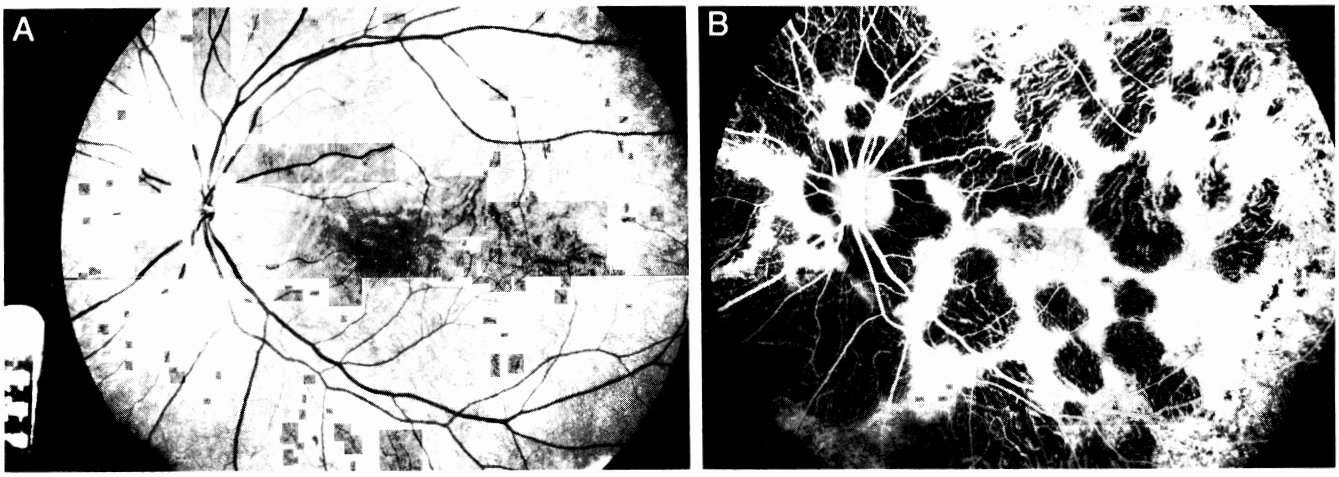

FIG 62–2.
Bietti's crystalline retinal dystrophy in a 45-year-old man with no family history; his visual acuity was OD 20/20, OS 20/25; the ERG was abnormal in a rod-cone pattern; and the light peak–dark trough ratio on the electro-oculogram (EOG) was 1.2. **A,** wide-angle red-free photography shows cyrstalline dots throughout the posterior pole and more apparent choroidal circulation than usual. **B,** FA of the same area reveals lobule loss of choriocapillaris with retention of larger choroidal vessels. In Bietti's dystrophy, the choriocapillaris loss is usually confined to the posterior pole.

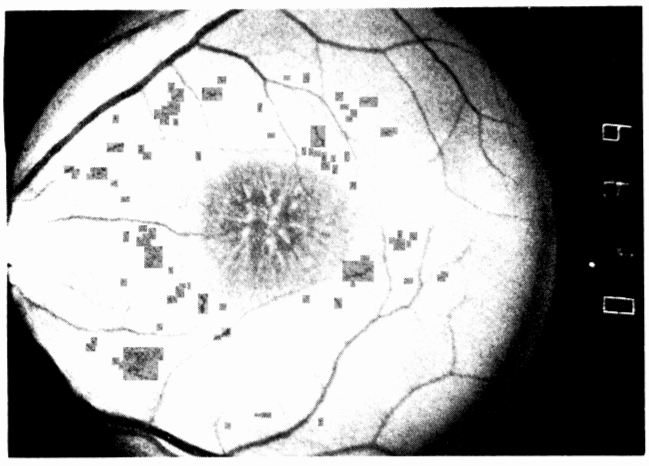

FIG 62–3.
Juvenile retinoschisis. A red-free fundus photograph of a 38-year-old man demonstrates a stellate pattern in the macula. Red-free photography most clearly demonstrates the macular schisis pattern characteristic of this disorder.

the midequator, but there is also an associated pigmentary retinopathy.

Confirming Macular Schisis vs. Edema

Cystoid macular edema is a known complication that may occur in a number of panretinal degenerations including RP. Occasionally a patient with the appearance of cystoid edema on direct ophthalmoscopy will be found to have no accumulation of dye in the foveal area on late frames of the FA. Stereo observation will usually demonstrate a schisis-like breakdown of the retinal tissue that may look cystic. The most common conditions where this may occur are Goldmann-Favre disease, juvenile retinoschisis, and Usher's syndrome. The lack of late macular staining in these cases can be most helpful in arriving at a better understanding of the patient's visual acuity problems.

X-linked retinoschisis has a distinctive ERG, although severe cases can be confused with RP, particularly if older members in the family develop a pigmentary retinopathy.[12, 20] The negative waveform in the dark-adapted bright-flash ERG may be ignored in the face of concurrent poor photopic and scotopic rod tracings. However, the macular and, if present, the peripheral schisis changes can be distinctive although at times subtle. Red-free photography, which is part of the usual FA protocol, often gives the clearest demonstration of macular schisis, which is reinforced by no staining or leakage in the area, so that the changes are not mistaken for cystoid macular edema (Fig 62–3). The presence of macular schisis on red-free photos in face of a negative wave would eliminate the diagnosis of congenital stationary night blindness, which also has a negative waveform (see Table 61–3).

The other common retinal dystrophy that occasionally has foveal schisis-like degeneration, i.e., a cystoid macular change without leakage, is Usher's syndrome[6] (Fig 62–4). Many of these patients demonstrate cystic-like changes that look like cystoid edema but do not show leakage on FA.[11] In these cases the macular cysts eventually degenerate and leave an atrophic macula.

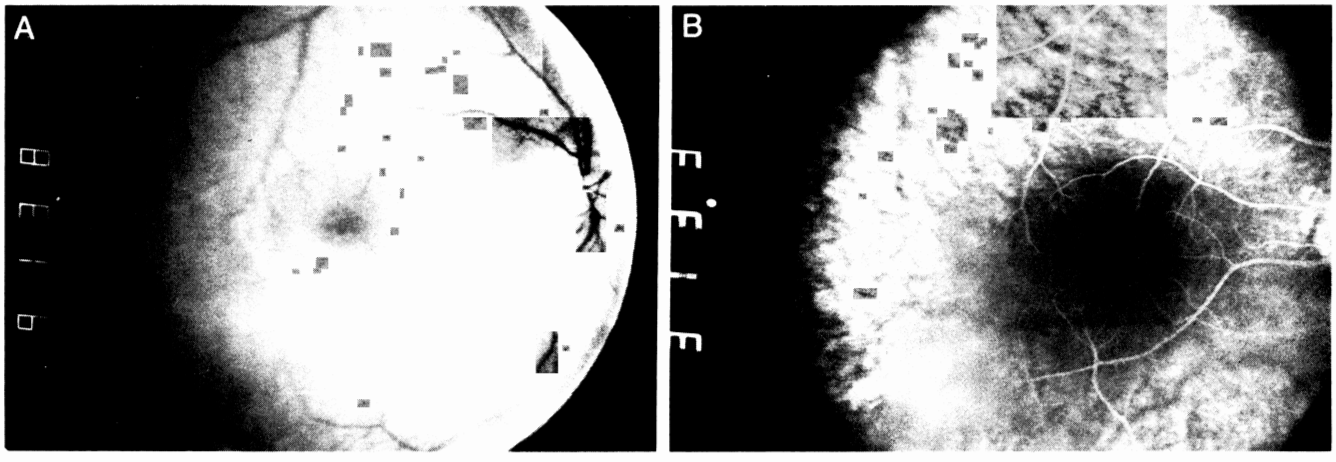

FIG 62–4.
Twenty-five-year-old man with Usher syndrome, type I. **A,** a red-free photograph demonstrates cysticlike macular changes. **B,** FA shows no late leakage in the macular area. Careful inspection of the fovea with the 90-D lens showed irregular cystic disintegration.

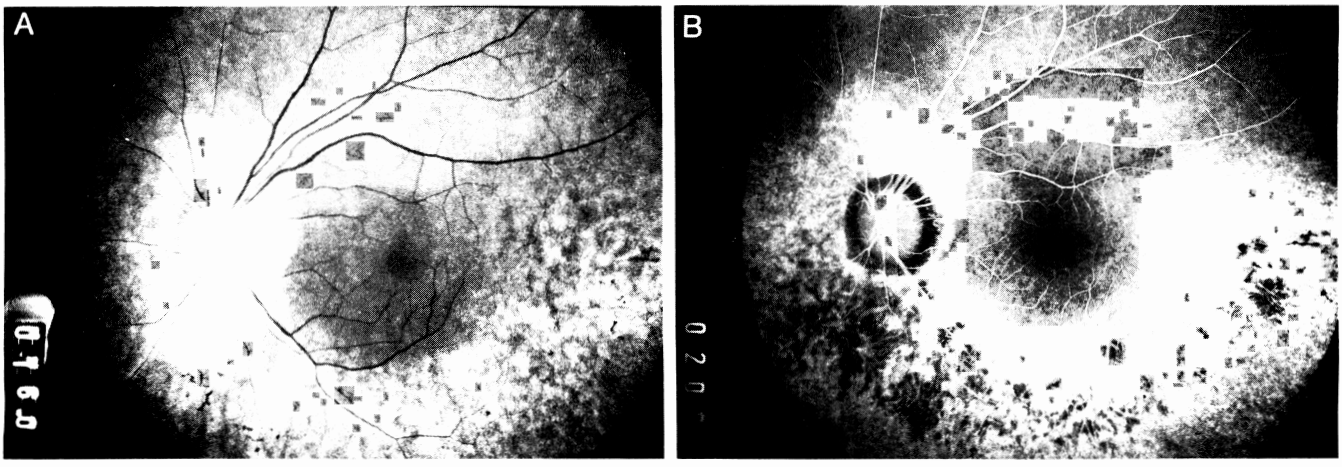

FIG 62–5.
Red-free photograph **(A)** and FA **(B)** of a 63-year-old woman with sector RP. The patient reported a 4-year history of visual symptoms and superior field loss. The RPE loss is evident inferior to the vascular arcade on FA.

Deutman reported five pedigrees with dominant cystoid macular edema in which the older individuals had atrophic macular degeneration while younger members had cystoid edema.[3] Moderate to high hyperopia, astigmatism, strabismus, and punctate opacities in the vitreous were common. Capillaries of the posterior pole and disc were dilated; the ERG was normal, and the EOG was subnormal.

Pattern Dystrophies/RPE Disease

FA is particularly useful in bringing out subtle lesions of the RPE and therefore can be quite useful in evaluating patients with hereditary macular dystrophies such as cone-rod, cone, or the pattern dystrophies.[3] Similarly, more subtle cases of sector RP can be diagnosed because there is often a clear demarcation line between apparently unaffected (or functioning) retina and areas of nonfunctioning retina (Fig 62–5). Wide-angle FA may be helpful in this documentation. While the FA would not be used alone in making the diagnosis, some carrier states might be identified such as choroideremia, X-linked ocular albinism, or RP. Early dominant type II RP will often show heavy granularity and focal dropout of the RPE and telangiectasia of the posterior pole and disc vessels before there are significant ERG changes.

Preserved Para-arteriolar Retinal Pigment Epithelial Retinitis Pigmentosa

In 1981, Heckenlively described an autosomal recessive form of RP that, in more advanced states, is characterized by preserved para-arteriolar RPE (PPRPE) adjacent and under retinal arterioles; diffuse atrophy of surrounding RPE is necessary in order to observe the PPRPE pattern.[8] Patients have been uniformly hypermetropic when typical RP patients are myopic, and the age of onset has usually been childhood to adolescent years. Many of the cases have had disc drusen. The ERG, when present, is in a rod-cone pattern, and the rod threshold on dark adaptometry is elevated. These patients tend to be severely affected by the time the PPRPE pattern is apparent.

FA is very effective in bringing out subtle cases of the PPRPE pattern (Fig 62–6,A), which may be difficult to distinguish on fundus examination alone. It should be noted that cases of diffuse retinal edema in advanced RP may occasionally show hypofluorescence next to arterioles, which could be confused with PPRPE (Fig 62–6,B).

Dark Choroid Effect

Bonnin et al. described a "silent choroid sign" in tapetoretinal degenerations that since has been termed the *dark choroid effect* or *sign*.[1] Histopathological correlation by Eagle and associates in a case of fundus flavimaculatus with dark choroid demonstrated lipofuscin-like deposits filling the RPE, thereby blocking the choroidal fluorescence.[4] The importance of this diagnostic sign was clarified by Fish et al. in 1981, who examined 91 patients with various types of hereditary macular disease with FA.[5] Forty-seven patients in the study had retinal

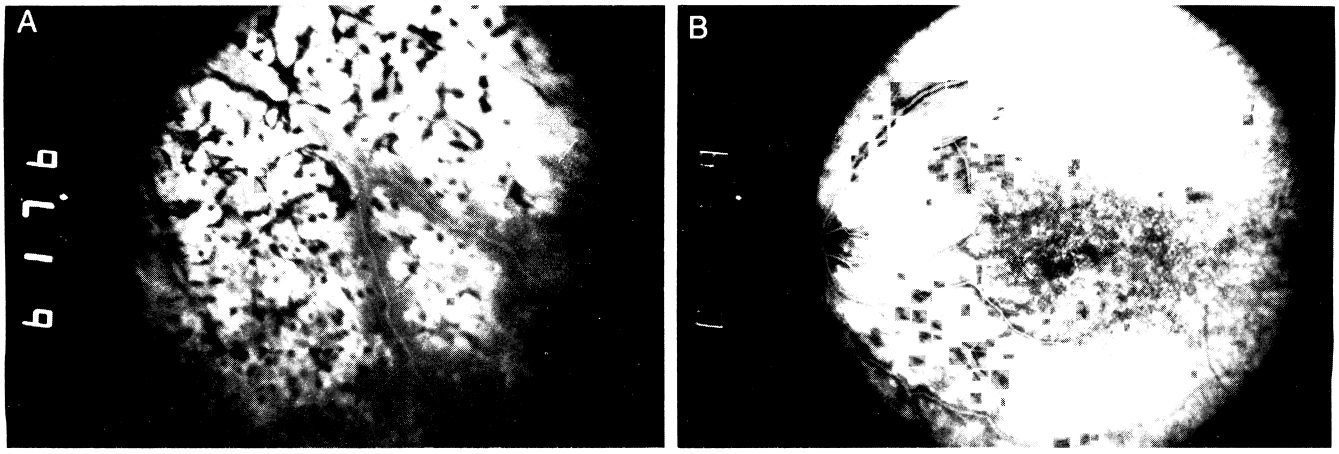

FIG 62–6.
A, FA in PPRPE in a 33-year-old lady with advanced RP from a family with consanguineous parents and presumed autosomal recessive inheritance. **B,** autosomal dominant RP patient who does not have PPRPE but has severe posterior pole edema where perivascular hypofluorescent changes which mimic fluorescein changes seen in PPRPE RP.

flecks, 34 of whom had a dark choroid effect. An additional 3 retinal dystrophy patients had the effect.

As suggested by the study of Fish et al., the most common retinal condition with dark choroid is fundus flavimaculatus (Fig 62–7,A and B), but occasionally recessive cone dystrophies or cases with inverse RP starting with posterior pole flecks will show the dark choroid effect, particularly in areas surrounding the macular area, and the dark choroid helps to identify this group of diseases. Some patients with RP have hypofluorescent fovea centralis areas on FA that likely represent the same process as dark choroid, that is, blockage of choroidal flush by thickened or less transmissive RPE.

While patients with fundus flavimaculatus typically have only mild or subnormal ERG and EOG values, some more advanced cases may have macular atrophy with minimal flecks and cone-rod ERG patterns, and the FA finding of dark choroid and full peripheral visual fields helps to establish the correct diagnosis. Some of these latter patients may be diagnosed as having central areolar choroidal sclerosis, but if a dark choroid effect is present, then the diagnosis of fundus flavimaculatus is more likely.

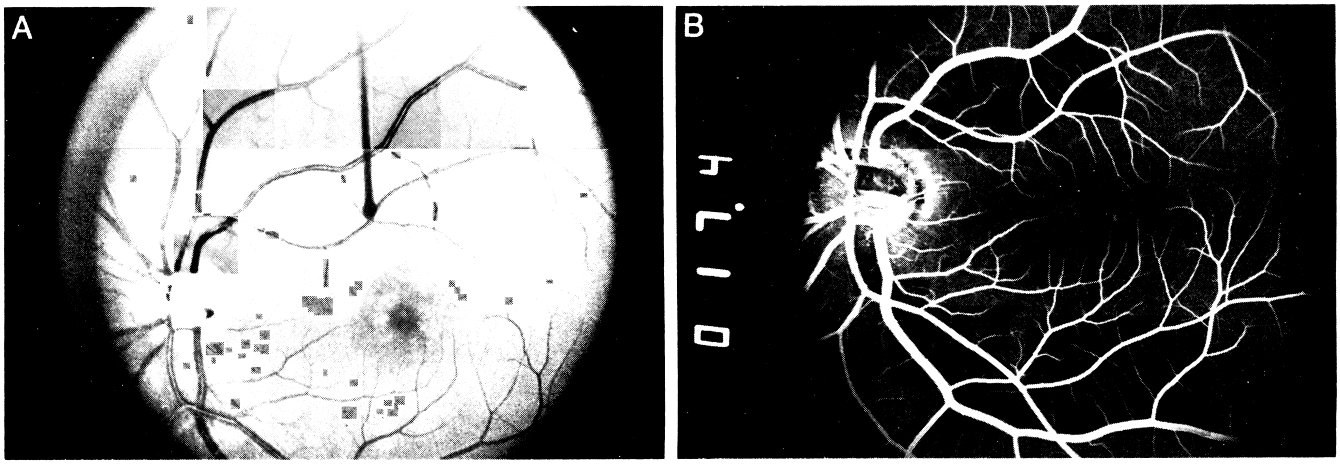

FIG 62–7.
Dark choroid effect in Stargardt's disease. **A,** red-free photography of a 22-year-old woman with 20/200 vision since 11 years of age demonstrates subtle macular atrophy and a few foveal flecks. **B,** FA shows profound hypofluorescence with only faint window defects in the macular area.

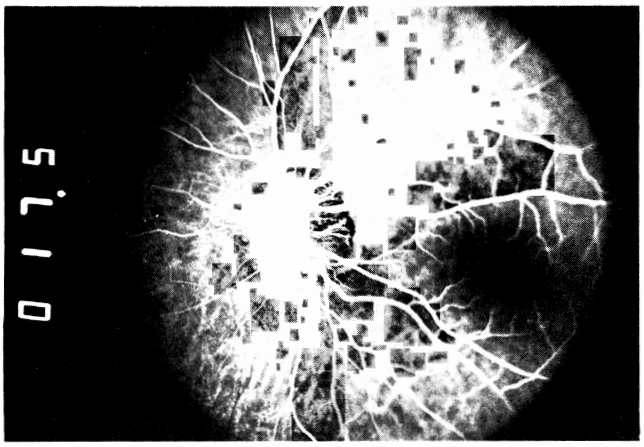

FIG 62–8.
Temporal optic atrophy and disc telangiectasia in a 33-year-old woman with RP cone-rod degeneration. Temporal optic atrophy may be seen in cone dystrophy, cone-rod degenerations, and congenital stationary night blindness; it is a strong indication to do an ERG if other symptoms are present. Temporal atrophy may be difficult to distinguish from tilted discs of high myopia, but FA often shows papillary vessels in the area where disc tissue should be present.[15]

Other Findings on the Fluorescein Angiogram

FA may assist in better understanding the ocular status of patients with a number of retinal degenerations since in advanced stages many will have diffuse retinal or macular edema. In other cases window defects may be seen that may not be obvious on clinical examination and indicate areas of atrophy or scarring. A nonspecific finding in a number of retinal dystrophies in early stages is telangiectasia of the optic nerve head and sometimes the macular area. This appears to occur more frequently in the cone-rod degenerations[1] or cone degenerations. Some patients with retinal dystrophy will also have marked hyperfluorescent disc staining on late phases, which on an otherwise normal examination may be an indication to pursue a diagnosis with electrophysiological testing. Optic nerve temporal atrophy has been reported in a number of diseases and may be more easily seen in some patients by FA[10, 14, 15] (Fig 62–8).

Rarely patients with retinal dystrophy will have subretinal or retinal neovascularization, leaking or telangiectatic vessels giving retinal edema or even a Coats' exudative reaction, all of which can be better understood with FA.[9, 21] Of particular importance to find are patients with RP and the Coats' reaction, who should be treated with photocoagulation, since if present the retinal or subretinal neovascularization may hemorrhage and lead to severe scarring and even phthisis bulbi (Fig 62–9).

Peripheral retinal telangiectasia is a prominent feature of facioscapulohumeral muscular dystrophy with deafness, an autosomal dominant disorder with variable expressivity.[7] Likewise, dominant exudative vitreoretinopathy is a hereditary dystrophy

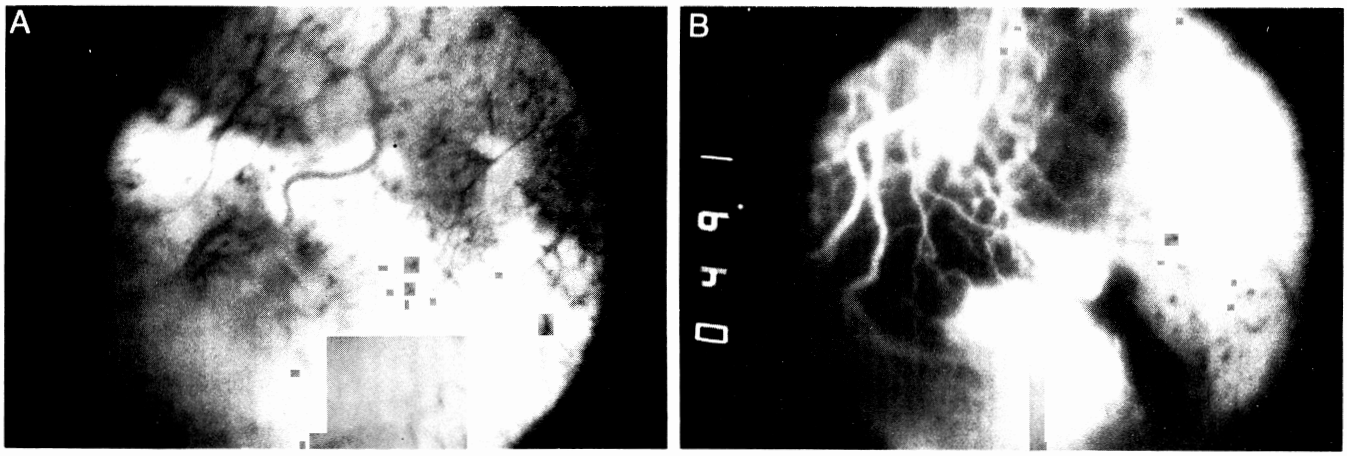

FIG 62–9.
Coats's reaction in a 32-year-old woman with advanced simplex RP. **A,** red-free photography shows pigmentation, subretinal exudates, and dilated retinal vessels. **B,** FA demonstrates telangiectasia and neovascularization. Initially, she responded to xexon photocoagulation with regression for 2 years, after which despite several photocoagulation treatments, the neovascularization progressed with vitreal hemorrhage and phthisis bulbi. Early subretinal neovascularization was found in her other eye, which regressed with panretinal photocoagulation.

that has prominent vascular changes.[16] Retinal electrophysiological studies have not been reported in this disease.

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