Principles and Practice of Clinical Electrophysiology of Vision

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Bietti's Crystalline Dystrophy of the Cornea and Retina

Richard G. Weleber
David J. Wilson

HISTORY OF THE DISEASE

In 1937 Bietti[3, 4] described three cases of retinal degeneration beginning in the third decade of life that was characterized by glittering crystals in the posterior pole and in the superficial paralimbal cornea. Welch[23] first used the term *crystalline retinopathy*, which so aptly describes the most characteristic feature of this disease. Although most accepted cases have crystals in both the cornea and retina, some patients who are otherwise typical lack the crystals in the cornea.[9, 13, 19] As recently reviewed by Wilson et al.,[24] over 77 cases have been reported worldwide. Heterogeneity most probably exists for Bietti's crystalline dystrophy, with the electrophysiological findings being of major significance in differentiating a diffuse type (Figs 90–1 to 90–3, Plate 17),[2, 3, 24, 26] with a profoundly abnormal electroretinogram (ERG), from a regional or localized type (Figs 90–4 to 90–7, Plate 18), with a more intact ERG that may be either normal or only mildly abnormal (Fig 90–8).[13, 22, 24, 26]

CLINICAL DESCRIPTION AND NATURAL HISTORY

Little information has been assembled on the natural history of Bietti's crystalline dystrophy, especially with regard to consideration of the two possible subtypes. Patients report an onset of symptoms anywhere from the second to the sixth decade of life, with the great majority in the third decade of life.[22] When patients are first examined, their Snellen visual acuity may be relatively good, but as paracentral scotomas develop, deepen, and enlarge, near visual tasks such as reading become progressively more difficult. Symptoms related to paracentral scotomas may exist early but often are difficult for patients to verbalize other than that their central vision is blurred or that reading is difficult. With the diffuse type, early symptoms are indicative of diffuse photoreceptor abnormalities. Night blindness and symptoms related to a loss of peripheral visual field are prominent, whereas with the localized or regional type patients become symptomatic from scotomas close to fixation, which are generally perceived as central vision loss. In both types, the scotomas correspond to the areas of retinal pigment epithelium (RPE) and choriocapillaris abnormalities. With the diffuse type, progression is more rapid, and the final visual impairment and subsequent disability are much greater (see Fig 90–3). Color vision can be abnormal in both diffuse and regional disease and is usually of the tritan type.[24–26]

The fundus appearance is different between the two types. In the diffuse type, tiny yellow crystals

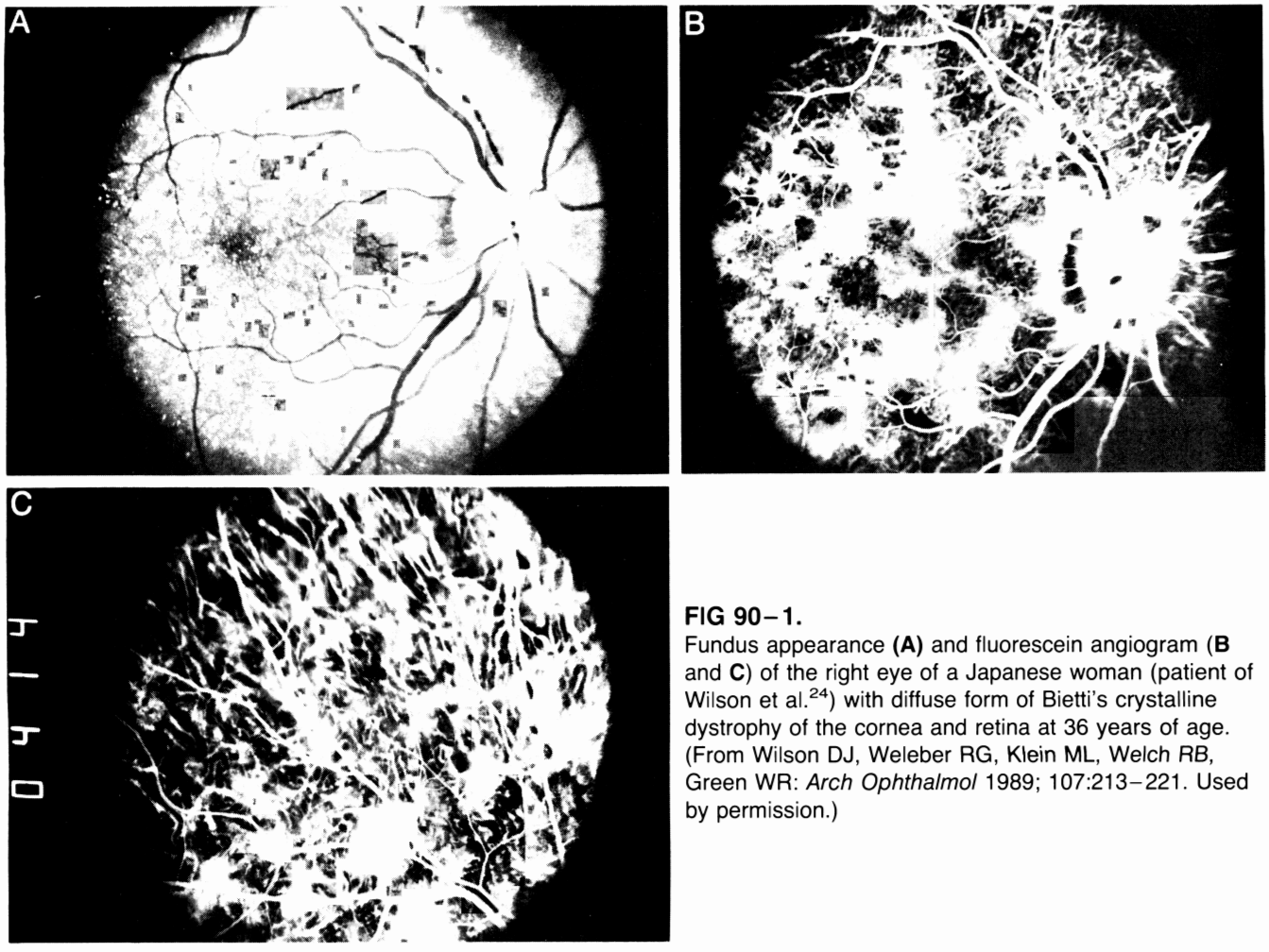

FIG 90–1.
Fundus appearance **(A)** and fluorescein angiogram (**B** and **C**) of the right eye of a Japanese woman (patient of Wilson et al.[24]) with diffuse form of Bietti's crystalline dystrophy of the cornea and retina at 36 years of age. (From Wilson DJ, Weleber RG, Klein ML, Welch *RB,* Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.)

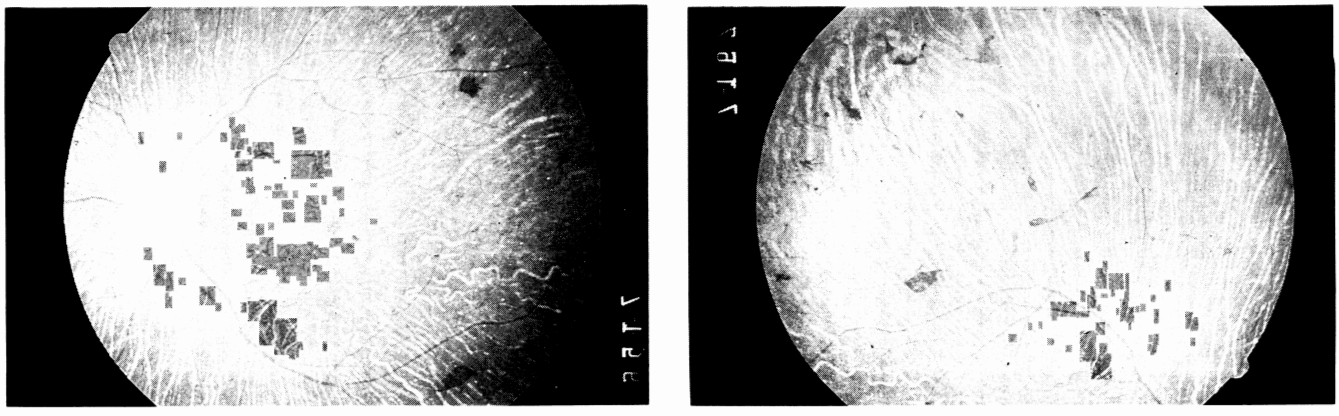

FIG 90–2.
Same patient as in Figure 90–1 at 45 years of age (**A** and **B**). Note the further loss of pigment epithelium and choriocapillaris over the 9-year interval. (From Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.) **(See also Color Plate 17).**

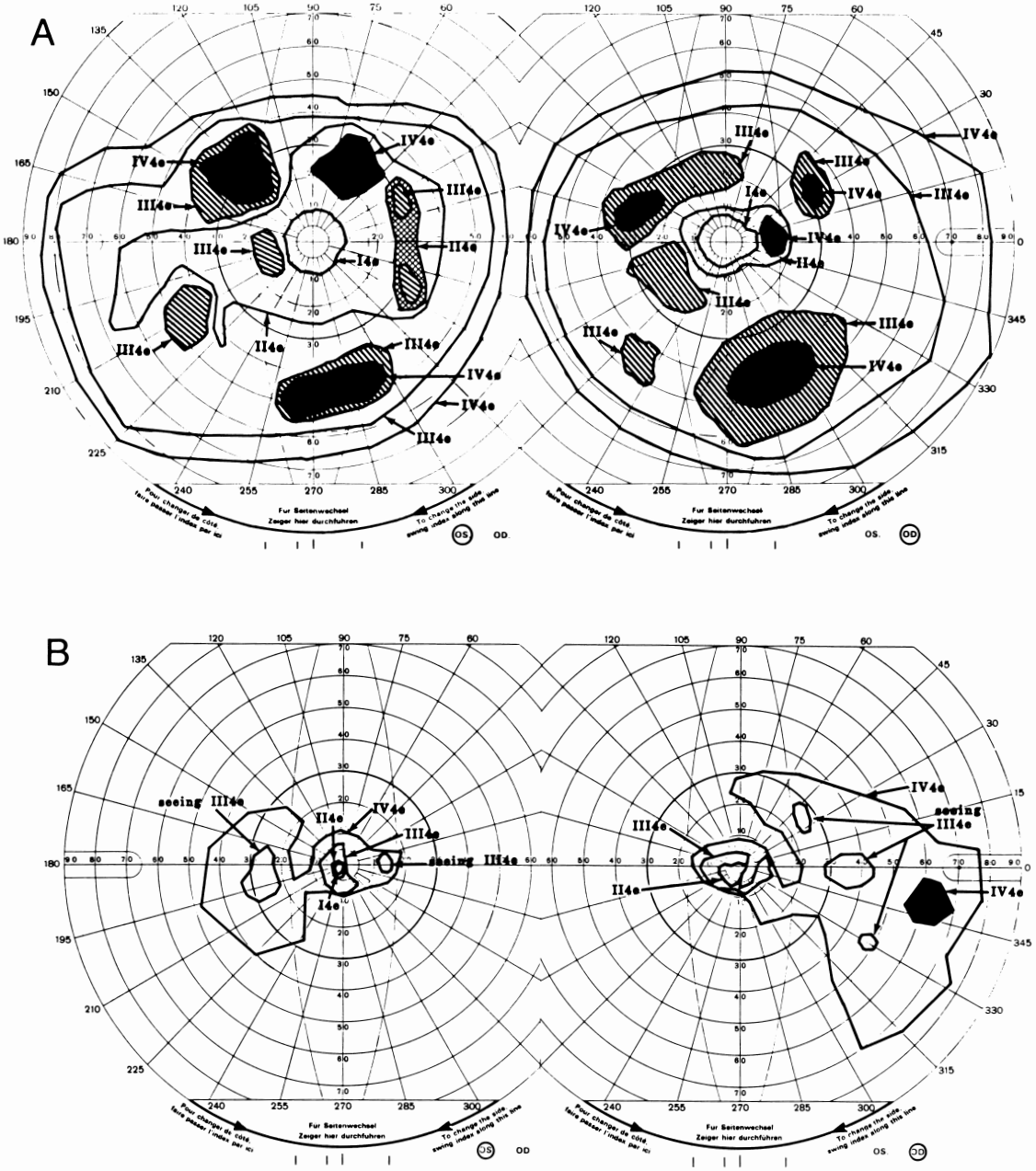

FIG 90–3.
Goldmann perimetric visual fields for the patient shown in Figure 90–1 with the diffuse form of Bietti's dystrophy at 36 **(A)** and 45 **(B)** years of age. Her visual acuity decreased from 20/30, J1 OU at 36 years of age to 20/50 J1 OU at 47 years of age. From 47 to 48 years of age, her visual acuity dropped to finger counting at 4 ft OD and 7 ft OS; she was unable to read any Jaeger type at near distance. (From Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.)

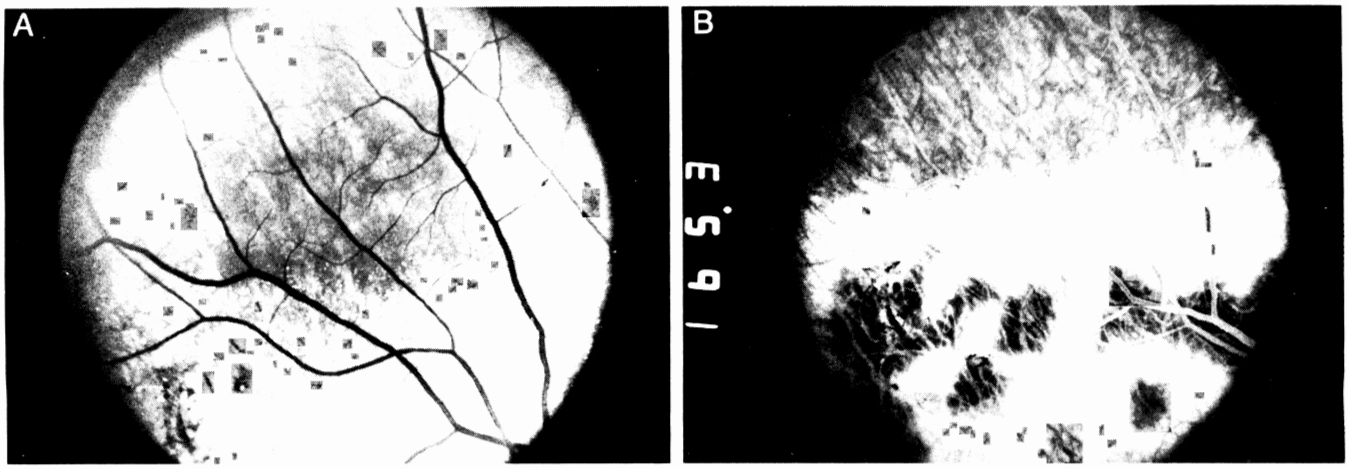

FIG 90–4.
Fundus appearance **(A)** and fluorescein angiogram **(B)** of the superior border of atrophic lesions in the posterior pole of the right eye of a 52-year-old man with the regional form of Bietti's crystalline dystrophy (patient 2 in Wilson et al.[24]). Note *that* crystals are prominent in the transition zone of disturbed RPE between atrophic retina and normal peripheral retina.

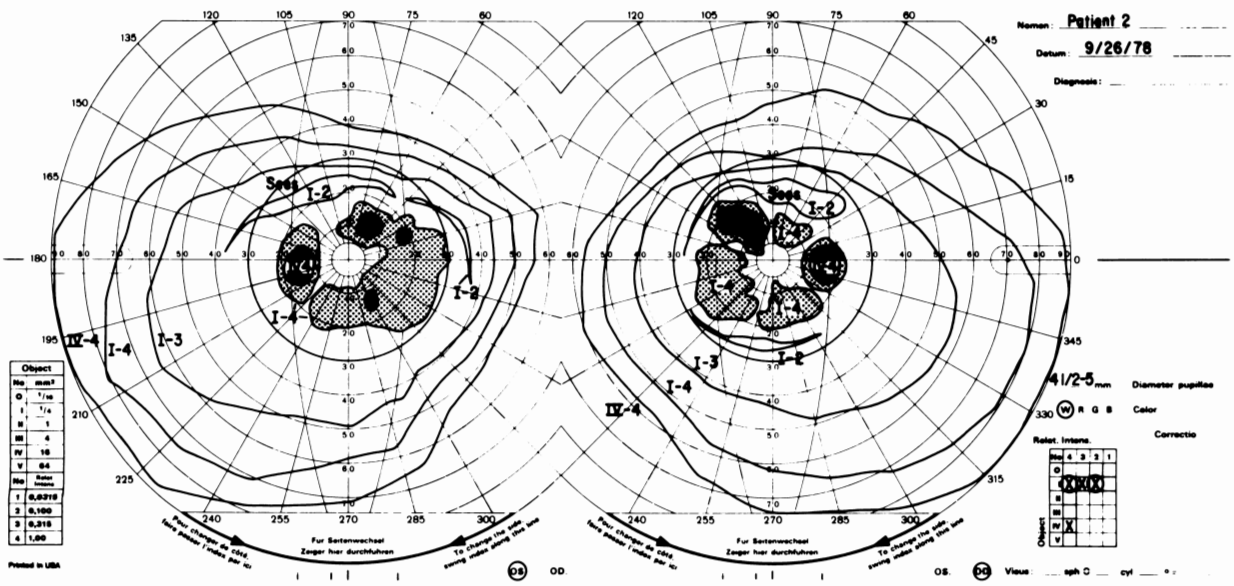

FIG 90–5.
Goldman perimetric visual fields of a 49-year-old man with the regional form of Bietti's crystalline dystrophy (patient 2 in Wilson et al.[24])—same patient as shown in Figure 90–4. Although his visual acuity was 20/25 in each eye, the patient was greatly bothered by pericentral scotomas.

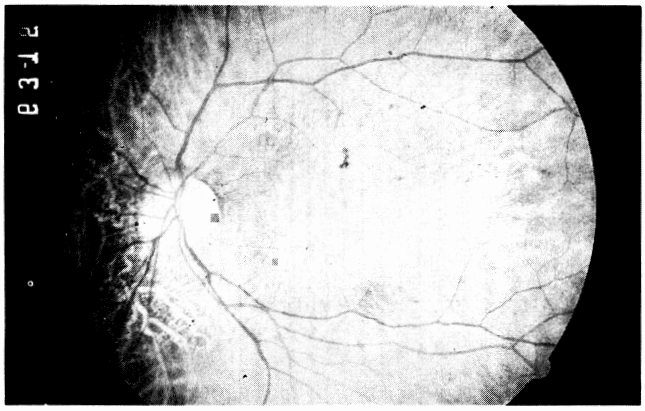

FIG 90–6.
Fundus appearance of a 61-year-old man with the regional form of Bietti's crystalline dystrophy (patient 3 in Wilson et al.[24]). **(See also Color Plate 18.)**

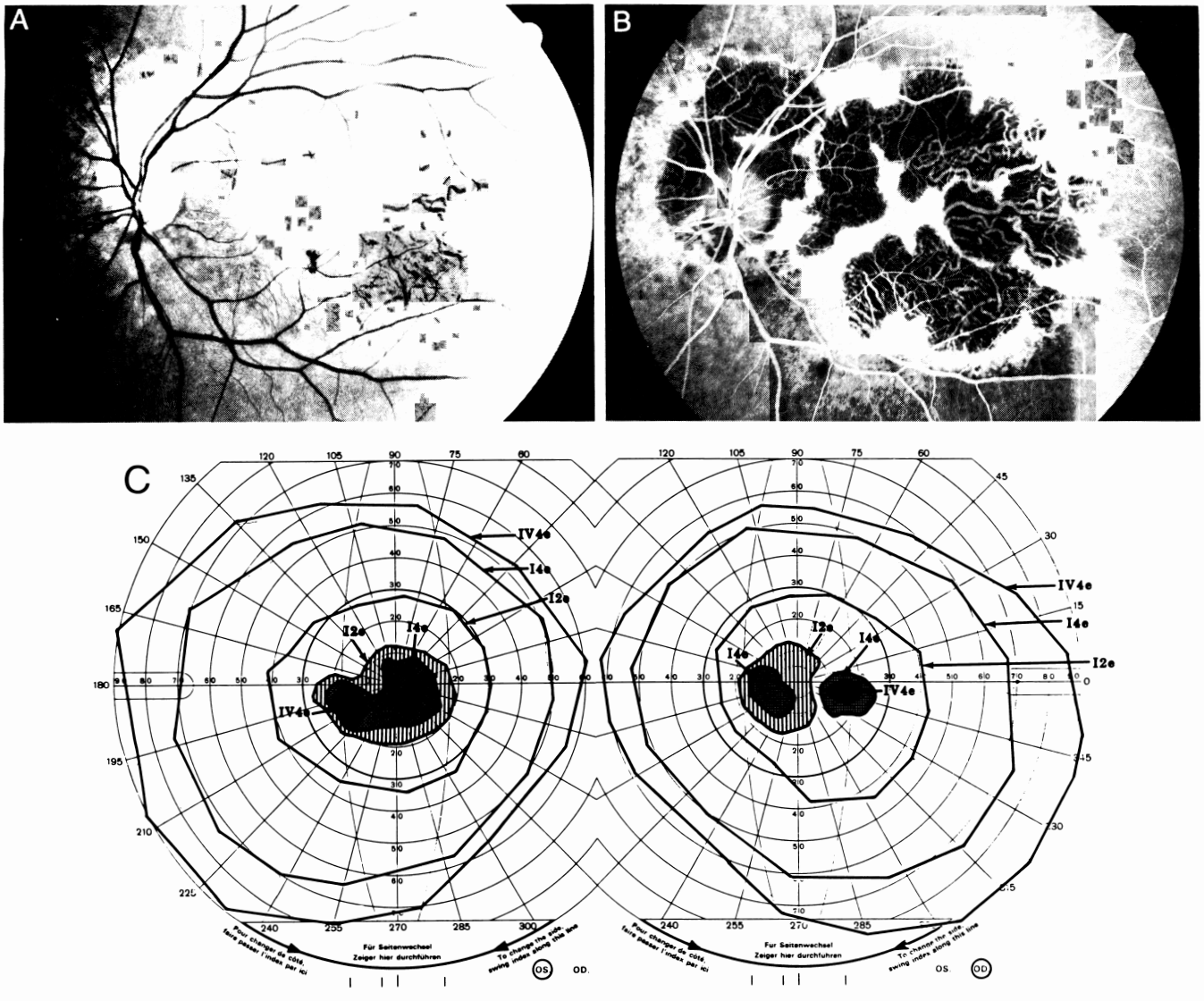

FIG 90–7.
Fundus appearance **(A)** and fluorescein angiogram **(B)** of the left eye and Goldmann perimetric visual fields **(C)** for the patient in Figure 90–6 (patient 3 in Wilson et al.[24]). The visual fields had not changed over those determined 9 years previously, but the visual acuity had decreased from 20/30 J1 to 20/40- J2.

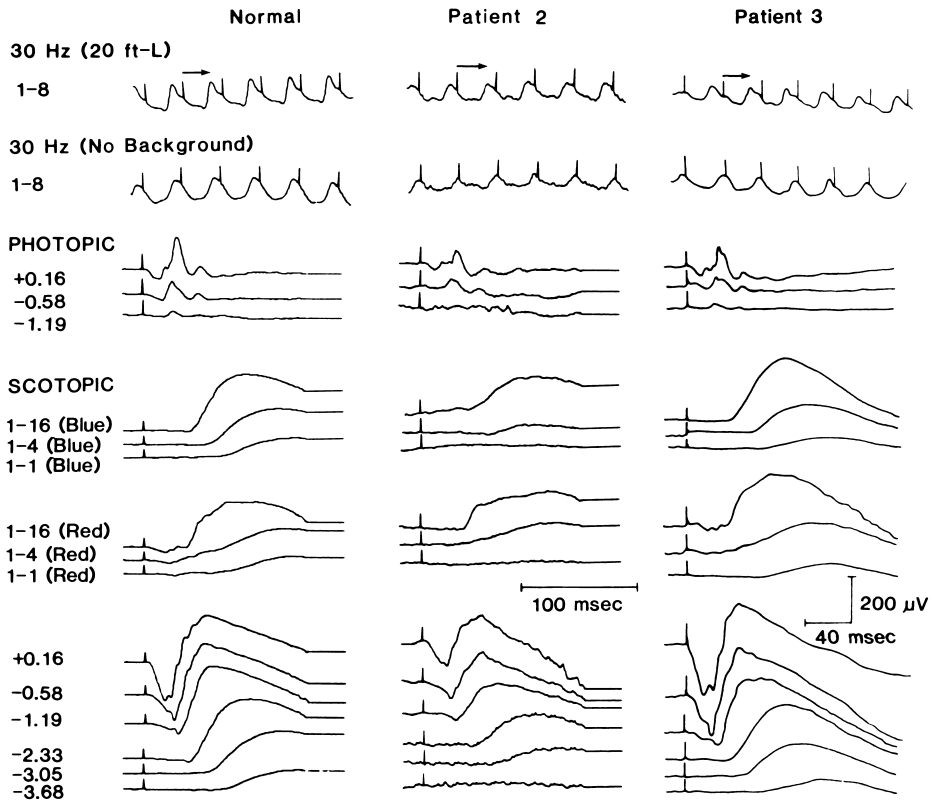

FIG 90–8.
Ganzfeld ERGs of two patients with the regional form of Bietti's crystalline dystrophy (patients 2 and 3 in Wilson et al.[24]) as compared with a normal ERG on left. ERGs from the right and left eyes were averaged to produce the tracings shown for the normal individual and patient 2. The stimulus spikes for the 30-Hz flicker and the photopic and scotopic responses for the normal ERG and patient 2 were set at 50, 50, and 75 μV and 75, 75, and 100 μV, respectively, to provide a vertical calibration scale. For these tracings the 100-ms horizontal scale applies. For patient 3 the calibration scale is noted for 40 ms and 200 μV. The numbers to the left of the normal waveforms preceded by a plus or a minus sign indicate the intensity of the white light stimulus in log foot-lambert-seconds. For the red and blue light responses the numbers indicate the photostimulator intensity settings. (From Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.)

are present at various levels in the retina, and RPE defects with pigment mottling and deposition can be seen diffusely throughout the fundus. In the localized or regional type, the disease begins in the posterior pole as RPE defects. Subsequent atrophy of the choriocapillaris leads to a prominence of medium and larger choroidal vessels. With fluorescein angiography a zone of hyperfluorescence will often separate involved retina from more normal appearing peripheral retina (see Figs 90–4 and 90–7, Plate 18). The regional type progresses by slow extension of the areas of RPE involvement and hyperfluorescence to further atrophy of the RPE and choroid into these regions.

The concept of subtypes of Bietti's dystrophy has only recently been considered, and many have previously explained the wide range of clinical manifestations by other means. For example, three stages of evolution have been proposed to explain the disparity of clinical involvement seen with Bietti's crystalline dystrophy.[26] Stage 1 involved primarily RPE disease. Stage 2 involved subsequent localized atrophy of the choriocapillaris. Stage 3 involved diffuse atrophy of the choriocapillaris. Presumably all patients progress from stage 1 to stage 2, but no case has ever been reported to progress from purely regional disease with preservation of normal peripheral retina to diffuse disease of the entire fundus. This observation has led us to propose that two subtypes of the disease exist.

The corneal lesions are very fine, whitish yellow crystals that appear just inside the limbus in superficial stroma and often require high magnification for detection (Fig 90–9). With time, the crystals become

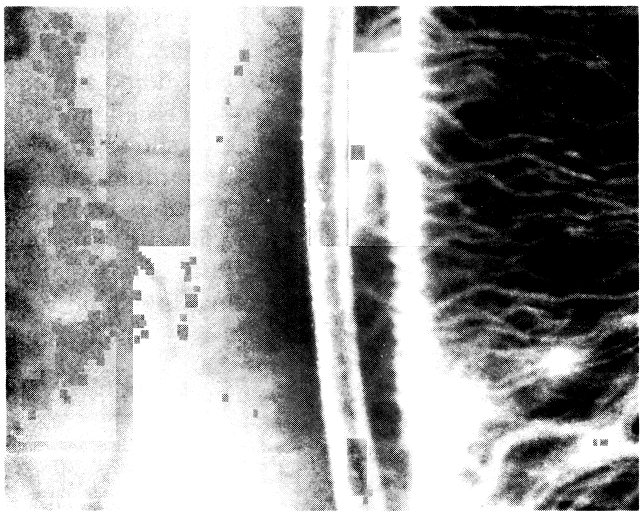

FIG 90–9.
Corneal crystals in the peripheral corneal stroma of the right eye of a 54-year-old man with regional retinal involvement (patient 2 in Wilson et al.[24]). (From Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.)

less apparent. Unlike those seen with nephropathic infantile cystinosis, the crystals are not visible within the more central cornea or the conjunctiva on biomicroscopy.

Reports of affected siblings, both males and females affected, and the high frequency of consanguinity among parents[2, 8, 9, 13–15, 26] who are otherwise normal strongly argue for autosomal recessive inheritance.

KNOWN HISTOPATHOLOGY/ PATHOPHYSIOLOGY OF THE DISEASE

Histopathology

On biopsy, crystals that have the appearance of cholesterol or cholesterol ester are present within corneal and conjunctival fibroblasts (Fig 90–10).[24] Complex lipid inclusions are also present. Wilson et al. have demonstrated inclusions in circulating lymphocytes that are similar to those seen in the cornea (Fig 90–11), which suggests that this disorder may represent a systemic abnormality of lipid metabolism.[24]

Physiology

Although the finding of inclusions in circulating lymphocytes suggests a systemic defect of lipid metabolism, no consistent abnormalities have been found with routine laboratory evaluations, including plasma and urine levels of amino acids, plasma lipoprotein and steroid determination, serum protein electrophoresis and immunoelectrophoresis, and leukocyte cellular cystine assay. Mild elevations of serum cholesterol levels have been reported in some but not all of the patients, and the significance of such a finding in older patients is unclear.[2, 13, 22, 24]

At present nothing further is known about the pathophysiology of this disease. Whether the diffuse and regional subtypes are allelic, if they truly are different genetic defects, is unknown.

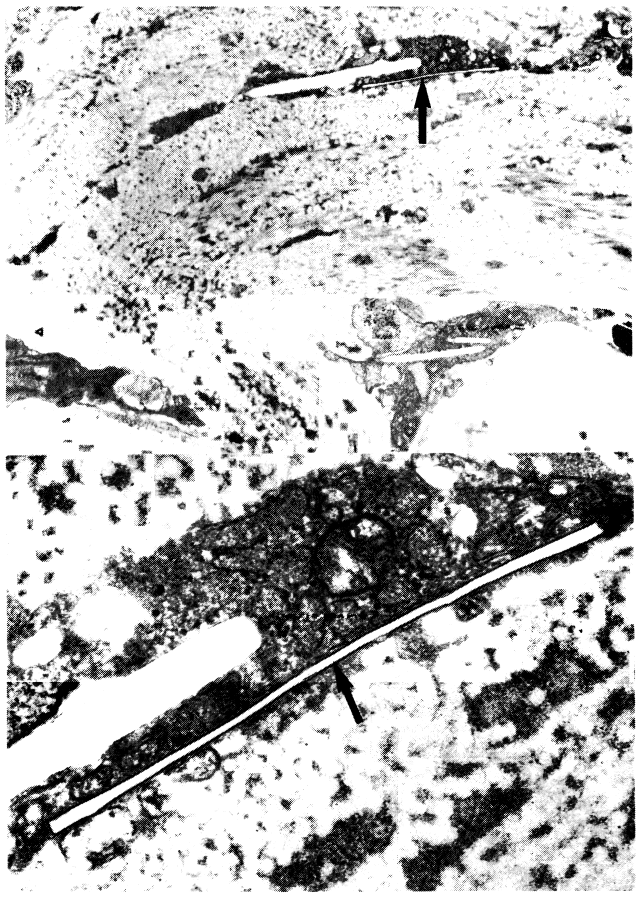

FIG 90–10.
Ultrastructural appearance of crystalline spaces *(arrows)* seen on a corneal biopsy specimen from a patient previously reported by Welch[23] (*top*, 13,000×; *bottom*, 64,000×.) (From Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.)

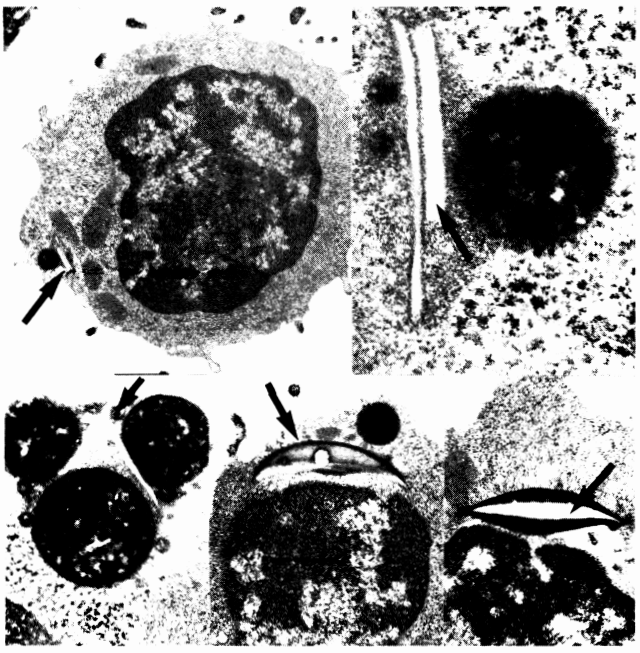

FIG 90–11.
Ultrastructural appearance of crystals seen in circulating lymphocytes (*top left*, 13,000×; *top right*, 110,000×; *bottom left*, 44,000×; *bottom center*, 20,000×; *bottom right*, 22,000×). (From Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: *Arch Ophthalmol* 1989; 107:213–221. Used by permission.)

RELEVANT TESTING AND FINDINGS

Since the diagnosis is easily made by the clinical examination, reports on affected individuals are often incomplete with regard to other studies. Few investigators have reported the results of extensive retinal function tests on patients with Bietti's dystrophy. Patients tend to fall into two groups: (1) those with regional disease, where the retinal function test results appear as one would predict when considering a localized process, and (2) those with diffuse disease, where the retinal function tests indicate widespread abnormalities. The ERG reflects the degree of involvement of the fundus. The ERG is low normal to moderately abnormal in the regional type[13, 22, 24, 26] and severely subnormal to nonrecordable in the diffuse type.[2, 24, 26] Negative ERGs have been reported.[2, 9] Although two-color static perimetry has not yet been reported on these patients, the finding of diffuse and regional forms of Bietti's dystrophy is similar to the recent classification of type I and type II dominant retinitis pigmentosa (RP).

The electro-oculogram (EOG) appears moderately abnormal early in diffuse disease but is low normal or only mildly abnormal in early disease of the regional type. Later, the EOG becomes abnormal in the regional type as well. One report noted the absence of fast oscillations of the EOG in a patient with regional disease.[24] Dark adaptometry shows an elevation of both the cone and rod portions of the curve, with minimal if any discernible cone-rod break. Further dark adaptation occurred in one patient with moderately advanced diffuse disease after patching for 14 hours, but the retinal threshold was still elevated 1.3 log units above that normally seen after 30 minutes.[24]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Bietti's crystalline dystrophy includes retinal oxalosis secondary to prolonged anesthesia with methoxyflurane,[6] cystinosis,[10, 21] canthaxanthine retinopathy,[5, 7] talc emboli,[1, 11] tamoxifen retinopathy,[17, 18, 20] and Sjögren-Larsson syndrome.[12, 16] The diagnosis of Bietti's dystrophy is almost always made or suspected on clinical grounds. Perimetry is performed to assess the extent of visual field loss and to allow correlation of fundus appearance with visual field defects. ERG appears to play a major role in defining diffuse from regional disease. EOG, dark adaptometry, and color vision tests are ancillary tests that help to establish the level and extent of retinal dysfunction and are useful in providing vocational and prognostic counseling and in following patients for the rate of progression.

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