Principles and Practice of Clinical Electrophysiology of Vision

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Cone Dystrophies and Dysfunction

John R. Heckenlively

Cone degeneration or dysfunction may be congenital or acquired, but the diagnosis is often difficult to make since the fundus changes can be subtle. The clinician may have little evidence to motivate asking for an electroretinogram (ERG), or even if suspicious, he may not realize that the ERG is the definitive diagnostic test. However, in some cases clinical signs and fundus changes provide strong diagnostic clues that a cone disorder may be present. Patients with cone dysfunction typically show uncorrectable subnormal vision, a history of photosensitivity or dark-to-light adaptation problems, a loss of hues or color vision (variable finding), and better sight at dusk or at night.[4] Frequently, patients do not volunteer these symptoms unless questioned directly for them.

Common fundus findings include a circumscribed granularity or atrophy of the macular area and temporal optic pallor or atrophy. In early cases there may be minor or no definite findings. Some patients with X-linked cone dystrophy have confluent areas of tapetal-like sheen, and a rare patient will have crystalline deposits in the macular area.

A diagnosis of cone degeneration or dysfunction is easily confirmed by ERG if standard protocols are followed so that the cone and rod systems are isolated and tested individually.[10] Besides using a single or averaged flash under light-adapted conditions, another technique for isolating the cone response is to employ a flickering, bright-stimulus light with a frequency greater than 20 to 30 cycles per second (hertz) since the rod response under standard conditions will attenuate fairly severely at 8 Hz and is absent by 20 to 30 Hz.[2, 7] The flicker stimulus, which maximally stimulates the cone system, is useful in bringing out subtle dysfunction or partial cone degenerations that may not be as apparent by single-flash techniques because the response is disproportionately worse than the single-flash photopic response.

Cone system dysfunction should be suspected in all patients who complain of photosensitivity, problems in light adaptation, and difficulties with color saturation or discrimination. Patients present with subnormal or abnormal visual acuity that is noncorrectable. A number of patients will have macular atrophy or degenerative changes, some of which start as bull's-eye macular lesions. Abnormal color vision is not an exclusive finding in cone degeneration and may be seen in macular degeneration without panretinal cone degeneration. Unless there is a known family history of a cone disorder, an ERG is needed to confirm the diagnosis of cone dysfunction since this diagnosis implies a panretinal disorder.

An important fact to remember is that the photopic ERG is normal in cases of focal foveal damage. The macular area contributes at most 10% to 15% to the photopic b-wave, so a larger reduction means that there is a greater involvement than the macula alone and, in many cases, often means that there is panretinal cone degeneration or dysfunction.[19]

TABLE 67–1.

Hereditary Forms of Cone Degeneration or Dysfunction

Congenital
Rod monochromatism (achromatopsia), autosomal recessive
Blue cone monochromatism, X-linked recessive
Later onset
Autosomal dominant cone dystrophy
Autosomal recessive cone dystrophy(ies)
X-linked recessive cone dystrophy with tapetal-like sheen[9]
X-linked recessive red cone dystrophy[16]

Traditionally the hereditary cone degenerations and dysfunction disorders have been classified into congenital or later-onset forms (Table 67–1).[2, 4] The two congenital cone dysfunction disorders, blue cone monochromatism, which is X-linked, and rod monochromatism, which is autosomal recessive, typically present with congenital nystagmus, and the diagnosis may be reported as "congenital nystagmus" unless an ERG is performed. A number of authors have been reluctant to term congenital cone disorders as dystrophies and have used "dysfunction" or dysfunction syndromes rather than a

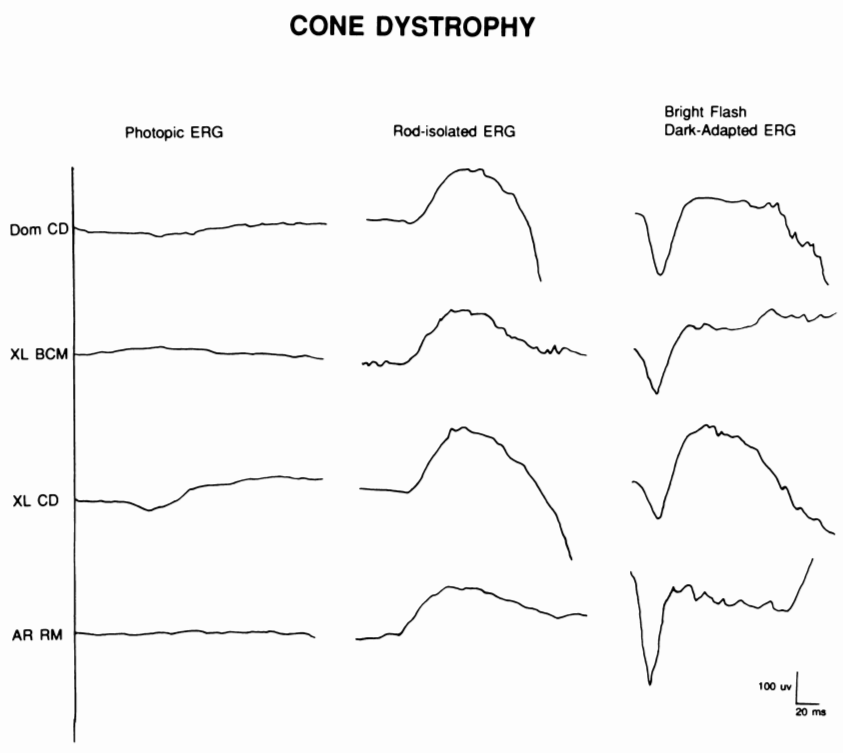

FIG 67–1.
A, ERG tracings of typical cases of cone dystrophy in which the photopic (cone) signal is nonrecordable *(left tracings);* in the rod-isolated signal, the ERG is well formed and is typically normal to subnormal *(center tracings).* The bright-flash dark-adapted tracing is subnormal to abnormal and, if interpreted alone without the other two tracings, would be misleading and not diagnostic of any condition. The cases illustrated here are a 54-year-old woman with dominantly inherited cone dystrophy *(Dom CD)* whose vision was OD 20/200 OD and 20/300 OS (see Fig 67–3,C); a 60-year-old man with X-linked blue cone monochromatism *(XL BCM)* who came from a large X-linked pedigree: his visual acuity as a young man was 20/60, but by 60 years of age it was 20/200 OU; a 58-year-old man with X-linked cone dystrophy *(XL CD)* with tapetal-like sheen (see Fig 67–3,A); and a 20-year-old woman with autosomal recessive rod monochromatism *(AR RM)* who presented with 20/200 vision. The ERG values for the above tracings are given in the following table.

	Photopic				Rod Isolated		Bright Flash Scotopic			
Condition	Aamp* (μV)	AIT (ms)	Bamp (μV)	BIT (ms)	Bamp (μV)	BIT (ms)	Aamp (μV)	AIT (ms)	Bamp (μV)	BIT (ms)
Dom CD*	NR				220	76	240	18	300	48
XLBCM	NR				170	90	128	21	240	57
XLCD	Late a-wave				240	78	130	22	320	58
ARRM	NR				230	90	351	20	304	51
Normal means†	90 ± 16	15 ± 1	170 ± 37	32 ± 1	349 ± 43	77 ± 4	274 ± 80	18 ± 2	484 ± 84	50 ± 5

*Dom CD = autosomal dominant cone dystrophy; XLBCM = X-linked recessive blue cone monochromatism; XLCD = X-linked recessive cone dystrophy with tapetal-like sheen; ARRM = autosomal recessive rod monochromatism; Aamp = a-wave amplitude; AIT = a-wave implicit time; Bamp = b-wave amplitude; BIT = b-wave implicit time; NR = not recorded.
†Normal control values are shown with standard deviations for a 35-year-old individual.

dystrophy or degeneration since no evidence has been found to date of a postnatal degeneration in these diseases. The term *dystrophy* has been broadly used in the medical literature, so it is not incorrect to use it in congenital-onset cone loss cases.

There are at least four later-onset hereditary types of cone dystrophy inherited in the autosomal dominant, autosomal recessive, and X-linked recessive modes.

The ERG pattern in all of these disorders is generally the same pattern (Fig 67–1): the photopic ERG is severely abnormal to nonrecordable by single-flash or computer-averaged methods, while the rod ERG is normal to subnormal (i.e., while the rod tracing may not have a normal amplitude, it is well formed and stable over time). Dark-adapted tracings frequently will show a blink response near the peak of the b-wave since most patients are photophobic. If a scotopic red flash stimulus is employed, the early cone response will be absent, and the later rod response will be present.

Conditions that can be confused initially with cone degeneration are early cases of type II or cone-rod retinitis pigmentosa (RP) or cases of RP inversa in which a cone-rod ERG pattern with a dense progressive central scotoma may be found and could otherwise be mistaken for a cone degeneration with mild rod involvement.[8] *Checking the peripheral visual field* is an important adjunctive test in all these disorders, and the field is typically stable and full over time. Visual fields, often performed serially, are an important confirmatory test for distinguishing cone disorders from progressive disorders with peripheral loss and may be diagnostic on the initial test. Some cone disorders will have central scotomas whose size is consistent with the level of visual acuity.

CLINICAL FEATURES OF CONE DEGENERATION

The diagnosis of cone degeneration or dysfunction can be extraordinarily difficult to make in the clinical setting since in many patients the signs and symptoms are very subtle. However, there are diagnostic indicators that ordinarily might be ignored and are presented below to aid in determining whether an ERG should be ordered to confirm the diagnosis (Table 67–2).

Early cases may be asymptomatic, or if vision is subnormal may even have nystagmus. The most common presenting symptoms of cone dysfunction are subnormal visual acuity and complaints of photosensitivity, loss of color saturation, or problems in adapting from a darkened environment to a lighted one. Some patients state that they see better at dusk or in the dark. An unusual symptom that a few city-dwelling patients with cone dystrophy may have is "urban night blindness"; in a city environment there is usually enough light at night that rods are unable to undergo full dark adaptation and cones do not function well. These patients will give a history of night blindness and from the symptoms mistakenly may be thought to have some form of RP. Another poorly understood group of patients who have urban night blindness are those who have rod-cone interaction dysfunction (Frumkes effect, see Chapter 59).

TABLE 67–2.

Signs and Symptoms Commonly Seen in Patients With Cone Degeneration

Presenting symptoms
Decreased visual acuity without obvious reason
Complaints of photosensitivity or glare
Color vision (often hue) problems
Problems in light or dark adaptation, particularly dark-to-lighted conditions
Central scotomas
Ophthalmoscopic signs of cone degeneration
Nerve fiber loss
Temporal optic nerve head atrophy or loss
Macular degeneration: early may appear granular; later occurs as symmetrical or round atrophy of the fovea centralis
X-linked later-onset degeneration has a tapetal-like retinal sheen

The most important sign to the clinician is that the patient's vision is not correctable to normal levels, and at times there may be no obvious reason for the visual deficit. Many patients will have obvious macular changes such as "bull's-eye" lesions (Fig 67–2,A and B, Color Plate 7) or macular atrophy, but there are other patterns to macular tissue loss that give clues that a panretinal cone degeneration is occurring.

One key to recognizing cone degeneration patterns of tissue loss is to note that in many patients the atrophy is confined to the fovea centralis[3] and usually is symmetrical between eyes (Fig 67–3,A–D, Color Plate 8); the tissue change itself may consist of diffuse loss, a confluent sheen, a granular pigmentary reaction, or even crystals. A few patients will have peripheral pigmentary deposits.[12] Concentric confluent loss in this pattern is not pathognomonic of cone degeneration but is a strong enough indicator to consider performing an ERG with a protocol that isolates cone and rod function.

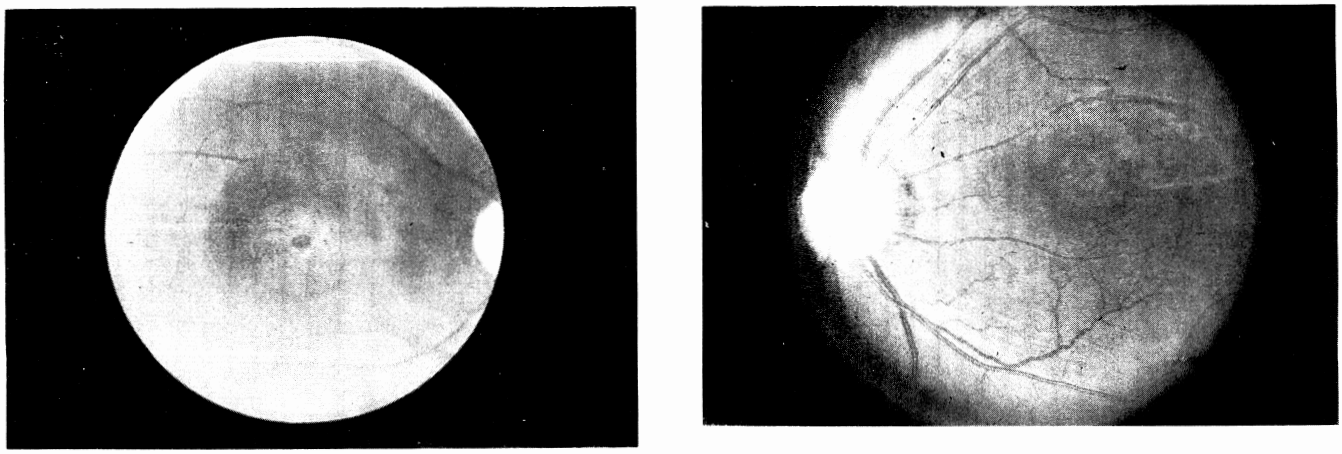

FIG 67–2.
A and **B,** bull's-eye macular lesion in an aunt and nephew, both in their early twenties, with autosomal dominant cone dystrophy. These patients' conditon could be mistaken for examples of Stargardt's disease or fundus flavimaculatus; the ERG will differentiate these retinal pigment epithelial diseases from cone degeneration. **(See also Color Plate 7.)**

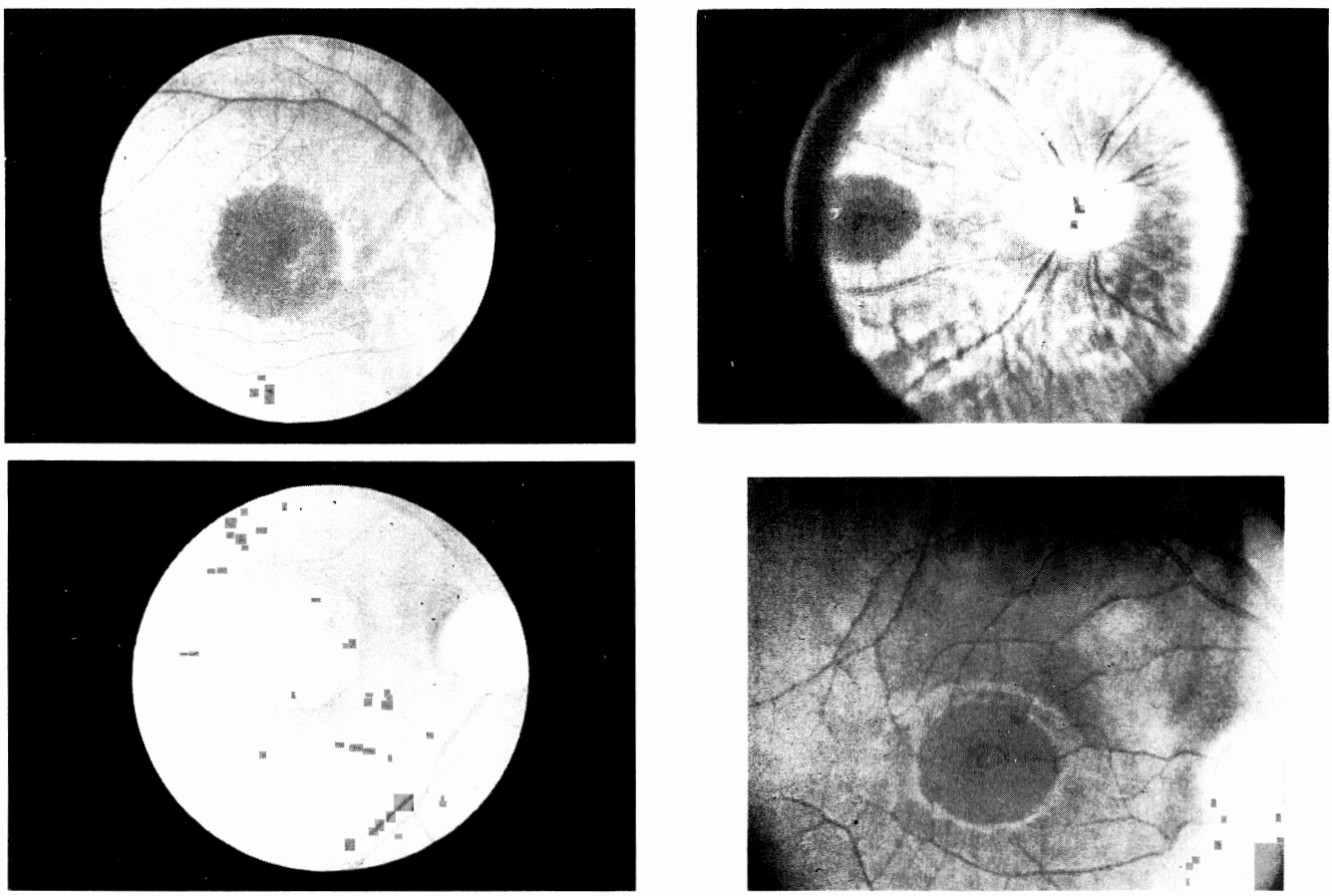

FIG 67–3.
Symmetrical, round atrophy of the fovea centralis is typically seen in a number of types of cone dystrophy or degeneration. **A,** a 54-year-old man with X-linked cone dystrophy and a tapetal-like sheen highlighting and surrounding the foveal atrophy. **B,** a 9-year-old boy with autosomal recessive rod monochromatism in which retinal surface reflections are lost in an area of symmetrical foveal atrophy. **C,** a 48-year-old woman with autosomal dominant cone dystrophy with macular atrophy. Many of these patients show hyperpigmentation of the retinal pigment epithelium at the edge of the macular atrophy. **D,** a 12-year-old boy with acquired sporadic cone degeneration with symmetrical foveal atrophy; retinal vessels curve into the depression caused by the atrophy as seen in Figure 67–3,B and D. **(See also Color Plate 8.)**

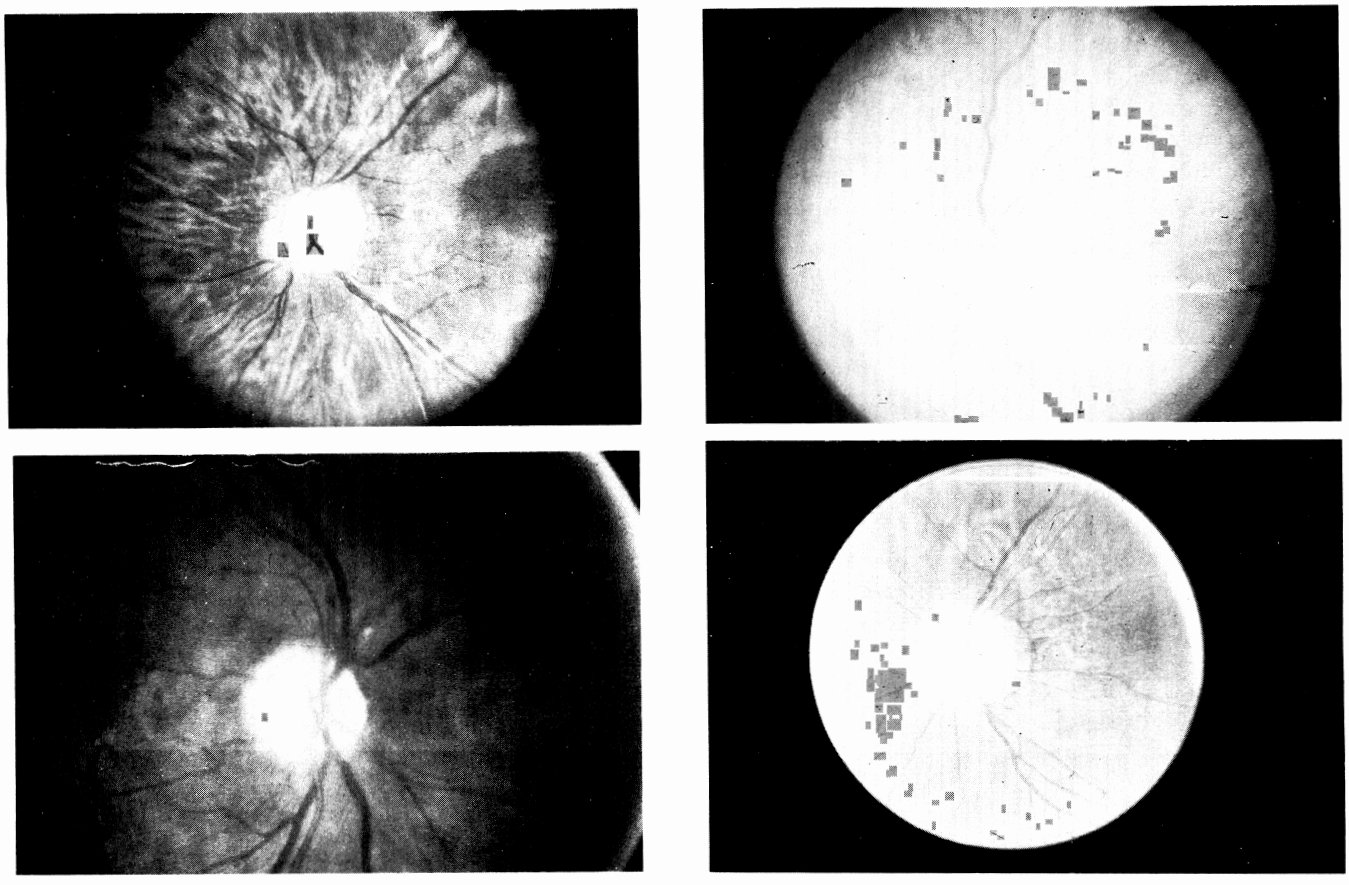

FIG 67–4.
Temporal optic atrophy in cone degeneration. **A,** a 9-year-old boy with rod monochromatism and temporal pallor. **B,** a 51-year-old man with blue cone monochromatism and a missing temporal disc. **C,** a 12-year-old boy with sporadic cone degeneration and a temporal wedge of pallor. **D,** a 28-year-old man with acquired cone degeneration and a granular glistening edge of the disc atrophy. This latter finding is occasionally seen in RP and, while similar to disc drusen, is localized temporally. **(See also Color Plate 9.)**

Patients with congenital-onset and most hereditary forms of cone dystrophy will have temporal optic atrophy (Fig 67–4,A and B, Color Plate 9) since many of these patients are myopic, the atrophy may be confused or misinterpreted as a tilted disc, or the change may be a combined effect of myopic alterations in scleral canal development and a loss of temporal disc tissue. Many of these patients, particularly those with a congenital-onset form, will demonstrate an abrupt loss of disc tissue that gives a flattened or squashed appearance to the temporal optic nerve head (Fig 67–4,B). Other patients will have distinct pallor of the temporal portion of the disc without obvious tissue loss (Fig 67–4,A), while adult-onset cone degeneration may have no disc changes.

Another pattern of disc atrophy that can be seen is a rim of white granular or sometimes crystalline-appearing material, often present in conjunction with disc pallor (Fig 67–4,C and D).

Nerve fiber layer loss is a final clue that a panretinal degeneration is present (see Figs 67–2,B and 67–3,C), but this is a nonspecific finding in a number of hereditary retinal degenerations.[14]

HEREDITARY FORMS OF CONE DYSFUNCTION OR DYSTROPHY

Rod monochromatism, often called achromatopsia, is inherited in the autosomal recessive fashion, but patients may have full to partial expression of the disorder, with visual acuity ranging from 20/60 to 20/200. There may also be varying amounts of nystagmus, which usually improves with age. This could imply that there are allelic or multiple forms of this entity. Since these patients typically have blond fundi and minimal granularity of the macula, they may be misdiagnosed as having ocular albinism, but

an ERG will quickly distinguish between the two diagnoses. Other methods that may be helpful include transillumination of the iris or performing lateralizing visually evoked responses.

Blue cone monochromatism is an X-linked recessive congenital cone dysfunction that tends to be milder than rod monochromatism (see Chapter 104). An X-linked recessive pattern of inheritance in the face of a congenital absence of cone function is a reliable indicator of this disease. A specific DNA probe or marker will no doubt be forthcoming shortly to help with diagnostic testing for this disorder because the gene is known to be on the long arm of the X chromosome (Xq28).[13] The use of special color vision test plates for differentiating males with blue cone monochromatism from those with rod monochromatism has been proposed.[1]

Patients with blue cone monochromatism may have visual acuity as good as 20/30 and occasionally as poor as 20/200; the macula develops a granular atrophy, and frequently there is severe temporal disc atrophy (Fig 67–4,B). Carriers for the disorder may show a loss of the cone portion (x-wave) of the red-stimulus dark-adapted ERG; the amount of loss is dependent on the degree of lyonization.

A late-onset X-linked cone dystrophy has been reported that has a characteristic tapetal-like sheen (see Chapter 105) and changes with dark adaptation (Mizuo-Nakamura effect).[9] These patients in later stages often will show a macular atrophy that is highlighted by the sheen (see Fig 67–3,A). As noted above, there is a pattern of symmetrical anatomical foveal tissue loss, and the sheen is missing from this area in this group of patients. Several of the affected family members have had round atrophic holes leading to retinal detachment, so these patients should be checked on a regular basis for hole formation, which will need laser prophylaxis if found.

An X-linked red cone degeneration has been reported in a pedigree in which the DNA analysis with a cDNA probe found a 6.5-kilobase deletion in the red cone pigment gene.[16] Clinically, patients have photosensitivity in childhood and a red color deficiency. The 15-year-old propositus's maternal grandfather and great-uncle had 20/200 vision with macular atrophy. The ERG showed a loss of red cone function, and the 30-Hz flicker appeared to be the most affected.

Autosomal dominant cone dystrophy in most families has a distinctive appearance and clinical history. Frequently subnormal vision will begin by the teenage years, and early macular atrophy will be seen.[11] At this stage the disease may be misdiagnosed as fundus flavimaculatus or Stargardt's disease, and some patients even have a few yellow deposits similar to flecks (see Chapter 89).[5] Patients aged 10 to 30 years may show cone ERGs that are barely recordable to extinguished, while in other families the cone ERGs will be only mildly affected. In all cases over time, however, the cone ERG progressively worsens and becomes nonrecordable by single-flash technique. In some cases flicker function may be worse than single-flash cone testing. These patients universally develop round, symmetrical macular atrophy (Fig 67–4,A and B). It is not known whether there is one or more gene sites for dominant cone dystrophy.

Linkage studies will eventually solve the question of the number of types of dominant cone dystrophy. It is of interest that benign concentric annular dystrophy on a follow-up report was found to demonstrate a slow cone degeneration which was inherited in the autosomal dominant fashion.[18]

Autosomal recessive forms of cone dystrophy clearly exist and have been reported in the literature, but this group of diseases is not well understood, in part because many cases appear as isolated occurrences and family studies are seldom productive.

PARTIAL CONE DEGENERATION OR DYSFUNCTION

A number of adult patients with cone degeneration and no family history will show subnormal vision, photosensitivity or complaints of light or dark adaptation, and foveal atrophy. A few patients will have golden or yellow deposits in the macular area. Some may have temporal disc atrophy. The cone ERG in some will be extinguished, while in many the cone signal will be partially recordable. In some patients the photopic ERG is greatly reduced while the rod signal is normal. In a few the single-flash cone signal may be normal to subnormal while the flicker response is greatly reduced. There is a wide variety of presenting visual acuities in these patients, but they typically range from 20/60 to 20/200. Some of these patients will have known dystrophies that are in evolution where the family history is not known, and others are idiopathic.

MANAGEMENT OF CONE DISORDERS

By the time patients with cone dysfunction are examined, most have discovered that tinted lenses are beneficial to their vision, both indoors and outdoors, although a few patients will not have tried sun-

glasses at all! The clinician can play an important role by emphasizing that patients with cone dysfunction do better on average than do patients with more progressive problems such as RP, and they can be given a more encouraging outlook. The ophthalmologist also can help by recommending to patients not doing so the use of multiple pairs of variably tinted lenses worn according to the lighting conditions. Particularly important is reassurance that wearing tinted glasses indoors is perfectly acceptable and necessary for their condition.

Once patients with retinal dystrophy learn that they have a problem that is considered untreatable, they often fail to seek ophthalmologic care, and refractive problems may be neglected. Since many patients with cone dystrophy have myopia, a current refraction is always in order. Patients with central scotomas and subnormal central vision may benefit from low visual aids and eccentric viewing.

Although there is no direct evidence that any drug therapy is beneficial in these conditions, experimental evidence indicates that antioxidants and radial oxygen-quenching vitamins such as vitamins C and E are useful in slowing animal hereditary retinal degenerations.[15] Studies localizing vitamin E found high concentrations in the photoreceptors and retinal pigment epithelium, and since vitamin E has a known antioxidant effect, supplemental vitamin E would appear appropriate.[6, 17] Thus these vitamins, which are generally nontoxic in prescribed doses, are a reasonable recommendation. Ultraviolet screening lenses would also be a reasonable recommendation, particularly in progressive forms of cone degeneration, in order to protect the retina from potential light toxicity.

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