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Cone and Rod Function in Cone Degenerations

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Progressive cone dystrophy (CD) is usually marked in the initial stages by reduced visual acuity, color vision deficiency and alterations in the photopic electroretinogram, while morphological alterations can be very mild; in some forms rods are affected in a later stage as well. We examined 40 patients with progressive cone dystrophy to determine the extent of functional losses in the cone system with psychophysical tests. A great variety of visual acuity and fundus alterations was found. Myopia was present in 74% of the patients. An autosomal dominant pattern of inheritance predominated (32%). No prevalence of gender was found. The age of onset ranged between 10 and 30 yr. All patients had progression of their symptoms. The total error score in color arrangement tests, the saturated Farnsworth Panel D-15 and the Farnsworth–Munsell 100-hue test, was pathologic with a predominance of confusions along the tritan and scotopic axis. Especially if visual acuity was below 0.5, color vision defects increased, but color vision defects were also found in patients with normal visual acuity. A general decrease of sensitivity in all three cone mechanisms was observed in measurements of spectral sensitivity. Moreover, cone–cone interaction as tested by transient tritanopia measurements was usually disturbed. In the dark adaptation function the threshold of the cone branch was usually elevated. These tests provide a good means to ascertain the correct diagnosis in early stages of the disease and to monitor progression in patients suffering from cone dystrophy. © 1997 Elsevier Science Ltd.

Color vision Cone dystrophy Cone flicker threshold Dark adaptation Psychophysics Spectral sensitivity Transient tritanopia

INTRODUCTION

The definition "dystrophy" implies an apparently normal morphology and function at birth, which progressively becomes worse during life (Krill & Deutman, 1972). Patients with progressive cone dystrophy, in general, have normal cone function in childhood and develop characteristic symptoms later in life. The three main symptoms are reduced visual acuity, increased glare sensitivity and poor color vision. The photopic ERG becomes pathologic and the symptoms show progression, which is one important point of differentiation from congenital achromatopsia and other stationary cone dystrophies such as blue cone monochromacy (Zrenner *et al.*, 1987; Reitner *et al.*, 1991; Winderickx *et al.*, 1992; Sadowski & Zrenner, 1994). After the initial reports by Knapp (1870) and Goodman *et al.* (1963), in large psychophysical and electrophysiological studies Berson *et al.* (1968) additionally found monophasic dark adaptation curves while rod thresholds were normal. They concluded that the absorption spectrum of the rhodopsin is normal. Krill & Deutman (1972) described two families that did not fit into the known categories of autosomal dominant macular dystrophies with macular abnormalities. Krill *et al.* (1973) reviewed the various diseases with diffuse or focal cone involvement. Krill & Deutman (1972), Krill *et al.* (1973) and Krill (1977) extensively described funduscopic findings in patients with cone–rod dystrophy. Functional impairment certainly precedes the fundus changes (Sloan & Brown, 1962). A correlation of the differences in fundus changes and psychophysical findings in patients with progressive generalized cone dystrophies was studied by Francois *et al.* (1976). Pokorny *et al.* (1979) classified cone dystrophies according to the pigment defects. Gouras *et al.* (1983) found a different type of retinal degeneration in two children with cone dystrophy, nyctalopia and supernormal rod responses. Several authors worked on visual field defects in cone dystrophies. Some (Sloan & Brown, 1962; Sloan & Feiocks, 1972; Jaeger *et al.*, 1979; Young *et al.*, 1982; Zrenner, 1987) pointed out that when using colored stimuli in perimetry and a higher background luminance of the Ganzfeld, cones are more selectively stimulated and a higher incidence of central scotomata might become evident. Goodman *et al.* (1963) gives different explanations for his detected variety of visual field defects. A lack of central scotoma can be due to

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unsteady fixation. Concentric constriction can be the consequence of a possible superimposed rod defect (see also Francois, 1977) which is confirmed by the electroretinogram in an involvement of the rods (Jaeger *et al.*, 1979) in more advanced cases. A ring scotoma, also observed by other authors (Francois, 1977; Grey *et al.*, 1977; Pagon, 1988; Weleber & Eisner, 1988) can be detected when some cone receptors remain present in the usually rod-free fovea according to Goodman *et al.* (1963). Ripps *et al.* (1987) assume an earlier and more severe affliction of midperipheral cones than central photoreceptors.

Findings in the literature concerning color vision are contradictionary; Steinmetz *et al.* (1956) mention tritanomaly in early stages of the disease, Ullerich *et al.* (1985) and Weleber & Eisner (1988) in advanced stages. Detailed psychophysical investigations of the function of individual cone mechanisms have very rarely been performed.

The purpose of this report is to describe the variation of psychophysical findings in a large group of patients with cone dystrophy. Special attention is given to color vision, visual acuity, spectral sensitivity, transient tritanopia, perimetry and dark adaptation together with the electrophysiological tests used to verify the diagnosis.

MATERIALS AND METHODS

In 40 patients with a mean age of 28 yr $\pm$ 23 yr at the time of examination, the diagnosis of cone dystrophy was established by taking the case history and applying the ophthalmological, electrophysiological and psychophysical methods described below. In the general ophthalmological investigation, slit lamp examination was performed besides the regular investigation of visual acuity, intraocular pressure, motility, pupil reaction and funduscopy. Perimetry was performed with an Octopus perimeter (program 21 or 31); dark adaptation and cone flicker thresholds were measured by means of a Tübingen Perimeter (details given below).

Color vision was tested with arrangement tests: the Farnsworth Panel D-15 (saturated) and the Farnsworth–Munsell 100-hue test. Additionally, to test cone function, spectral sensitivity was measured. Transient tritanopia was determined to assess the function of the cone–cone interaction as described below.

For electrophysiological tests the electrooculogram (EOG), the Ganzfeld electroretinogram (ERG) and the pattern electroretinogram (PERG) were used. The ERGs had been registrated according to the ISCEV-Standard (Marmor *et al.*, 1989): (1) rod b-wave: dark adapted, white flash of 3.9 mcd sec m^{-2}, six times every 0.5 sec; (2) maximal rod response: as (1) but using a flash of 2500 mcd sec m^{-2} with an interstimulus interval of 5 sec; (3) oscillatory potentials: conditions as for maximal response, using a band pass filter of 100–250 Hz; (4) after 10 min light adaptation (32 cd m^{-2}) registration of 30 Hz flicker response (2000 mcd sec m^{-2}); (5) single white flash cone b-wave was provoked by flashes of 2500 mcd sec m^{-2} with an interstimulus interval of 0.6 sec. The electrophysiological results of this group of patients were described in detail by Sadowski & Zrenner (1991); only a table that shows the electroretinographic results is presented later.

Spectral sensitivity

The psychophysical threshold for the perception of 30 monochromatic test lights with different wavelengths (400–710 nm) was used to determine spectral sensitivity. In an optical two-channel Maxwellian view system, monochromatic test lights with a diameter of 13 deg were superimposed on a white adaptation light of 15000 td and a diameter of 30 deg. The presentation of the monochromatic test light was controlled by a motor-driven monochromator, which determined the wavelength in 10 or 20 nm steps ranging from 400 to 710 nm. By means of an electromagnetic shutter, presentation time was set for $t = 400$ msec. The patient, with pupils dilated (Mydriaticum Roche) monocularly fixated in horizontal position the center of the adaptation light (marked by a hair cross) and was asked to press a button upon recognition of the test flash. The quantal energy of the test field, expressed in number of quanta per second and square micrometer retinal area, was regulated by a circular neutral density wedge. The threshold was calculated by presenting the stimulus eight times in an up and down staircase procedure. All functions were controlled by a computer (Minc 11/23, Digital Equipment), which also stored and calculated the results. The results were printed on a plotter (for details see Zrenner, 1983; Baier & Zrenner, 1984; Zrenner & Nowicki, 1985; Zrenner *et al.*, 1986a,b). Evaluation was done by comparing each patient's curve with the results of a control ($n = 6$) $\pm$ 1 SD.

The calibration of the optical system was repeatedly tested and the values were always within 1 SD. A smoothing function was fitted through neighboring points to reduce the influence of individual variation in the measurements. Because of the relative small number of patients tested and their individual results of sensitivities of maxima and minima, a statistical evaluation is not very useful. The result was deemed pathological if the patient's curve was not in the range of 1 SD of the control. The points of greatest interest were the maxima (B, G, R) and the minima (B/G, G/R). If there was no clear maximum or minimum, a value was taken in a spectral range of $\pm$10 nm around the expected wavelength position. Additionally, to determine the reliability of the results the mean $\pm$2 SD was calculated for the patients examined and compared with the mean $\pm$1 SD for the control population. The sensitivity of the minimum between middle- and long wavelength cones was elevated if the G- and R-peak resulted in one peak and it was also beyond the 1 SD range of the control (absolute measure).

Transient tritanopia

A change in the perception threshold for a blue test light (451 nm) in a period of 2 sec after extinction of a

yellow adaptation light (574 nm) was measured at several intervals and during a period of 300 msec with a yellow adaptation light (section 1 in Fig. 5). The stimulus was produced by the same two-channel Maxwellian view optical system described above. During the first few hundred milliseconds after the extinction of the yellow adaptation light (section 2 in Fig. 5) the threshold for the blue test light paradoxically increases, i.e., the sensitivity for the blue test light is lower than during the presence of the yellow adaptation light, although the light quanta of the yellow adaptation beam have too long a wavelength to affect the blue cone. Subsequently the threshold slowly decreases until it reaches its original value at about 1000 msec (after extinction of the adaptation light; section 3 in Fig. 5). This transient reduction of short wavelength sensitivity ("transient tritanopia") stems from interaction between long and short wavelength cones, which can be disturbed if there is an affect of long or short wavelength cones or of the transmitter or the lateral connection (Mollon & Polden, 1975; Mollon & Polden, 1979; Zrenner, 1982, 1983; Baier & Zrenner, 1984; Zrenner *et al.*, 1986a,b). The evaluation method of transient tritanopia is comparable to the evaluation method of spectral sensitivity. The criterion points (i.e., those of greatest interest) were chosen at −200, 0, 300 and 1300 msec.

Dark adaptation

Dark adaptation was tested with a "Tübingen perimeter". The pupil of one eye was dilated with "Mydriaticum Roche". Light adaptation to a white Ganzfeld of 850 cd/m^2 for 10 min preceded the measurement. After extinction of the adaptation light, a test stimulus with a diameter of 104 min was presented for 500 msec to the retina at a temporal eccentricity of 200 on the retina during monocular fixation, maintained by means of a red fixation mark in the center of the Ganzfeld globe. During a 30 min period of dark adaptation the test light was increased every minute from subthreshold values in steps of 0.1 log units until the patient responded by pressing a button as soon as the test spot was recognised. The resulting curve consists of two parts: the cones determine the threshold during the first 7–10 min of the measurement while after the cone–rod break the rods determine the threshold for the remainder of the test (see also Kohen *et al.*, 1985; Zrenner *et al.*, 1986a; Lorenz & Zrenner, 1987; Schneider & Zrenner, 1987; Zrenner, 1988).

RESULTS

In Table 1 the electroretinographic results of 31 patients with cone dystrophy recorded according to the ISCEV-Standard are shown (Marmor *et al.*, 1989). Besides rod response to weak single flashes, all amplitudes were reduced due to deterioration of the photopic system and implicit times were prolonged in maximal rod response, single flash cone response and oscillatory potentials (Sadowski & Zrenner, 1991).

Table 2 shows the 40 patients with the diagnosis of cone dystrophy who had been investigated. The age ranged between 5 and 61 yr (mean 30.5 yr) at the time of examination. All patients noticed first symptoms, such as a reduction of visual acuity and glare sensitivity, between the ages of 5 and 30 yr with a mean of 20 yr. Progression of the symptoms had been reported by each patient. No preference in the distribution of gender of the patients was found (22 females, 18 males). Refraction: myopia predominated with 75%, with a myopia larger than −3.0 D in 35%, followed by hyperopia (17.5%) and emmetropia (7.5%).

The optical media of all subjects were clear. Visual acuity of our patients with cone dystrophy ranged between 0.1 and 1.2. In 65% of our patients visual acuity was 0.5 or below, as shown in Fig. 1, where visual acuity is plotted against frequency. The remaining 35%

TABLE 1. Amplitudes and implicit times of patients with cone dystrophy are shown in comparison to the norm.

	Normals (±1 SD)	Patients with cone degeneration
Amplitude (μV)		
Rod b-wave	155 ± 37	130 ± 49
Maximal response	550 ± 85	318 ± 85
Oscillatory potentials	82 ± 16	30 ± 10
Flicker response	190 ± 40	53 ± 47
Single flash cone b-wave	200 ± 35	85 ± 30
Implicit time (msec)		
Rod b-wave	86 ± 4	79 ± 10
Maximal rod response	37 ± 5	44 ± 8
Oscillatory potentials	23 ± 0.5	20 ± 5
Flicker response	62 ± 1	35 ± 15
Single flash cone b-wave	34 ± 1.5	45 ± 10

In patients with cone dystrophy, amplitudes of cone responses, maximal rod responses and oscillatory potentials were reduced, implicit times of single flash cone responses and maximal rod responses were prolonged.

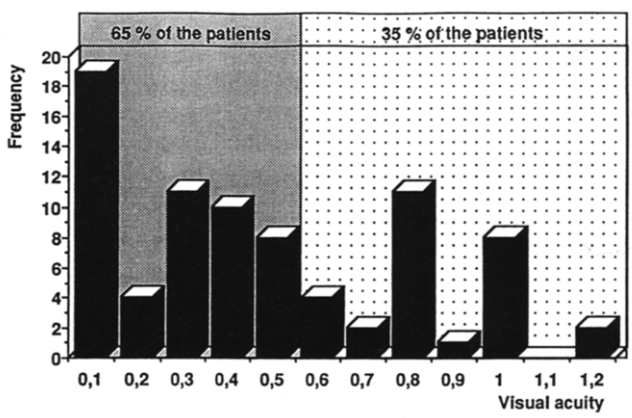

FIGURE 1. Visual acuity of 80 eyes of patients with cone dystrophy. The visual acuity is plotted against the number of eyes tested. Two-thirds (65%) of the patients had a visual acuity of 0.5 and below. Note that there are also patients with cone dystrophy who have normal visual acuity.

TABLE 2. Summary of the general ophthalmologic data of all patients investigated

	Patient	Age (y)	Sex	Visual acuity	Refraction	Fundus
1	B.A.	27	m	0.4/0.4	m	m
2	B.M.	32	m	0.8/0.8	m > 3.0sph	m
3	B.EK.	11	f	0.5/0.5	m	m
4	B.J.	32	m	0.4/0.8	m	—
5	D.Ch.	56	f	0.3/0.3	m	m
6	E.A.	24	m	0.1/0.1	m	m/o/p/v
7	G.T.	13	f	0.1/0.1	e	m/p/v
8	G.G.	22	f	0.8/0.6	m > 3.0sph	m/p/v
9	H.G.	34	f	0.8/0.8	m	m/o
10	H.L.	31	f	1.2/1.2	m	—
11	H.C.	21	f	0.3/0.4	h	-
12	H.AM.	15	f	1.0/0.8	m > 3.0sph	—
13	H.G.	27	f	0.2/0.1	m	m
14	H.H.	50	f	1.0/1.0	m	—
15	I.E.	20	f	0.1/0.1	h	m/p
16	K.JP.	9	m	0.4/0.4	h	m
17	K.A.	9	f	0.5/0.6	h	m
18	K.J.	48	m	0.8/0.8	m	m
19	K.E.	38	m	0.3/0.3	m	m/o/p
20	K.J.	14	f	0.8/0.9	m	m
21	L.I.	46	f	1.0/1.0	h	m
22	L.W.	40	f	1.0/1.0	m > 3.0sph	o/p
23	M.H.	48	m	0.6/0.5	m	m/p
24	M.J.	19	m	0.1/0.1	h	m
25	M.P.	39	f	0.5/0.2	m	m
26	N.R.	54	m	0.2/0.3	m	m/o/p
27	P.P.	15	m	0.3/0.3	h	m
28	R.E.	31	m	0.1/0.1	m	m/o/p
29	R.W.	61	m	0.3/0.1	m > 3.0sph	m/p
30	R.S.	12	f	0.7/0.3	m > 3.0sph	m
31	R.D.	23	f	0.1/0.2	m > 3.0sph	m/o
32	R.G.	18	f	0.1/0.1	m	m
33	Sch.H.	34	m	0.1/0.1	m	o
34	S.I.	61	f	0.7/0.8	m	m/p
35	T.H.	39	f	0.1/0.1	e	m/p
36	Wa.F	42	m	0.4/0.3	m	m/o
37	Wa.M.	34	m	0.5/0.5	e	m
38	W.F.	29	m	0.4/0.4	m > 3.0sph	m
39	Z.A.	5	f	0.6/1.0	m > 3.0sph	m
40	Z.P.	35	m	0.5/0.4	m > 3.0sph	m

Visual acuity data are given in the order: right eye/left eye. m, myopia; h, hyperopia; e, emmetropia. fundus, fundoscopic findings: only the pathological findings are marked. m, pigment alterations in the macula; o, palor of the optic disc; p, alterations of the fundus periphery; v, narrowing of retinal vessel. A normal fundus is indicated by "—".

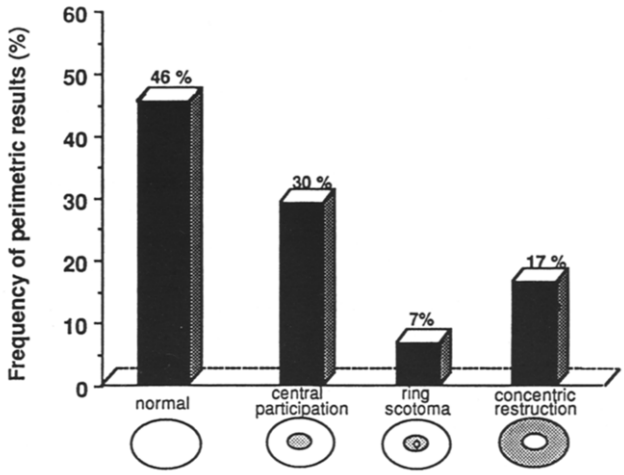

FIGURE 2. Percentage distribution of perimetric results of 58 eyes of patients with cone dystrophy tested with the Octopus perimeter (Program 21 or 31). The type of visual field changes are sketched by the circles, where the outer circle corresponds with the outer limits of the visual field and the inner circle with the macular area. Gray zones show scotomas. The bars demonstrate proportionally the percentage distribution, which is also indicated on the *y*-axis and above the bars. The patients' visual fields show a very variable pattern.

were distributed into equal parts of patients with visual acuity ranging between 0.6 and 0.8, and between 0.8 and 1.2.

Inheritance

In the majority of the 36 families involved (60%), the pattern of inheritance was very difficult to ascertain because of missing family members (due to death or war). A predominance of the autosomal dominant pattern of inheritance was found in 32% of the family trees. In 8% of our patients the disease was transmitted autosomal recessively. No patient was found in this group where an x-recessive mode of inheritance could be firmly established, although it could not be excluded in several families. In four families a second family member had been investigated.

Funduscopy

Fundus changes were usually very discrete and variable. Most pathological findings were found in the macula in form of pigment-alterations ("m", 83%). The fundus periphery ("p") was involved in 30% and the optic nerve head showed pallor ("o") in 26%. Retinal vessels were narrow ("v") in 6% of our patients. (See also Table 2.)

Perimetry

In Fig. 2 a general overview of the perimetric results performed with the Octopus perimeter (programme 21 or 31) of 58 eyes of our patients is given. The bars show the distribution of the different types of visual fields found in the patients, which are also symbolized below the bars. Fixation was controlled by monitoring. Interpretation of visual fields was given by three independent neuroophthalmologists and only visual fields with an identical interpretation were evaluated. Four different groups can be discerned according to the visual field defects. The largest group is represented by normal visual fields (46.5%). Among the pathological perimetric findings relative or absolute central scotomas predominated (30%). In four eyes (7%) the center had a normal light sensitivity, i.e., a ring scotoma was found. Seventeen percent of the patients showed a concentric constriction, which seems quite atypical for cone diseases. In the normal visual fields and those with concentric restriction a central participation would also be expected. These data suffer from the fact that the

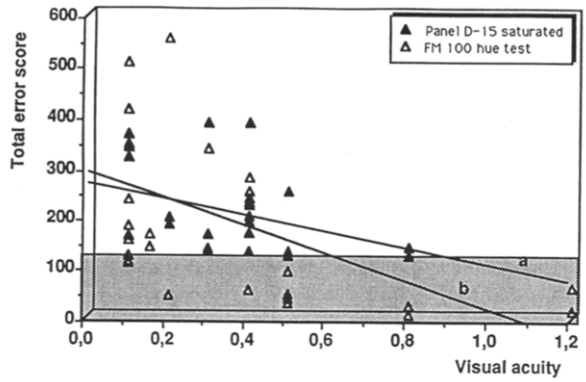

FIGURE 3. Results of arrangement tests, saturated Farnsworth Panel D-15 (23 eyes tested) and Farnsworth–Munsell 100-hue test (37 eyes) in patients with cone dystrophy. The visual acuity is plotted against the total error score. Filled triangles represent the Panel D-15 results, open triangles the results of the FM 100-hue test. The lines are the regression lines (a) = Panel D-15 test; (b) = FM 100-hue test. The minimal total error score for the Panel D-15 test is 117, indicated by the gray zone. In both tests the total error score increases with a decrease of visual acuity. This is dramatic when the visual acuity decreases to 0.5 or below. There are also patients with low visual acuity and good color vision.

background luminance of the Octopus perimeter is too low (1 cd m^{-2}). Rods do, therefore, contribute to a large extent to the threshold and cone pathology cannot be revealed, since the most sensitive receptor mechanism always determines the threshold. In retrospect we have to conclude that the Octopus perimeter is not suited to detect subtle cone pathology. Stimulation with colored test flashes, e.g., red, might result in a more selective cone stimulation. Certainly a higher background luminance (Goldmann standard etc.) would remove the effect that the visual field is determined by rods.

Color vision

Arrangement tests. The Farnsworth Panel saturated D-15 test, (in 23 eyes) and the Farnsworth–Munsell 100-hue test (in 37 eyes) were used for an initial assessment of color vision. The total error score was evaluated for both tests.

The total color difference score (TCDS) of the Farnsworth Panel D-15 tests was calculated from the CIELAB (1978) or CIE (1976) formula by a computer program (Bowman, 1982). The TCIDS has a minimum (no mistakes) of 117 (gray zone in Fig. 3) for the saturated form of the test. It increases with the number of transpositional crossovers on the D-15 score pattern (Bowman, 1982). However, it should be mentioned that this evaluation procedure does not differentiate different types of color vision defects according to confusion axis, in contrast to the Farnsworth–Munsell 100-hue test (Bowman, 1982; Pokorny *et al.*, 1979).

The Farnsworth–Munsell 100-hue test was analyzed with a computer program and, in addition, evaluated according to Kitahara (Pedriel, 1962; Pokorny *et al.*, 1979; Winston *et al.*, 1986; Kitahara *et al.*, 1989).

In Fig. 3, the patients' visual acuity is plotted against their total error scores for each of the two tests. In both tests the total error score increases dramatically with the decrease of the visual acuity to 0.5 and below, but it can also be normal with low visual acuity. On the other hand, patients with a quite good visual acuity can also have problems with color discrimination, but the total error score does not reach extremely pathological values in any of these patients; a good visual acuity is not a guarantee for good color vision in cone dystrophy.

TABLE 3. Percentage distribution of the frequency of total error score above the normal range in the Farnsworth–Munsell 100-hue test in relation to the axis of confusion

Axis of confusion	Frequency of total error score above the normal range in the FM 100 test (%)
Normal	20%
Protan	8%
Deutan	4%
Tritan	21%
Tetartan	0%
Scotopic	27%
Erratic	20%

Most mistakes are made in the tritan color axis (21%), the scotopic (27%) and the erratic axis (20%). Normal error scores were also found (20%).

The regression lines (calculated for the results of both tests; (a) = Farnsworth Panel D-15 test saturated form, (b) = Farnsworth–Munsell 100-hue test) mark the tendency of reduced error score with increasing visual acuity. The inclination of the regression line of the Farnsworth–Munsell 100-hue test (b) is slightly steeper.

The evaluation of the Farnsworth–Munsell 100-hue test according to Kitahara allows a differentiation for the axis of confusion. In Table 3 the distribution of different color vision deficiencies according to these axes is listed (37 eyes tested).

Most total error scores above the age-related norm were found in the tritan axis ($n = 8$, 21%), the scotopic axis ($n = 10$, 27%) and erratic axis ($n = 7$, 20%). Also normal tests were found ($n = 7$, 20%). Only very few patients made mistakes in the deutan ($n = 1$, 4%) and the protan axis ($n = 3$, 8%). The prevalence of the scotopic (and erratic pattern) means that an identification of colors is mainly determined by rods.

Spectral sensitivity

The spectral sensitivity was tested in 16 patients. This time-consuming measurement could not be performed in all patients because of age or time limitations and also too strong glare sensitivity and resulting fixation problems. The results are shown in Fig. 4, Table 4 and Table 5. In the presence of white adaptation light the normal spectral sensitivity function has three maxima that indicate the maxima of the three cone mechanisms (the short, medium and long wavelength-sensitive blue, green and red cone) as well as two minima (that indicate opponency) usually near 460 and 550 nm, where the two neighboring cone mechanisms inhibit each other (King-Smith & Carden, 1976; Sperling & Harwerth, 1971).

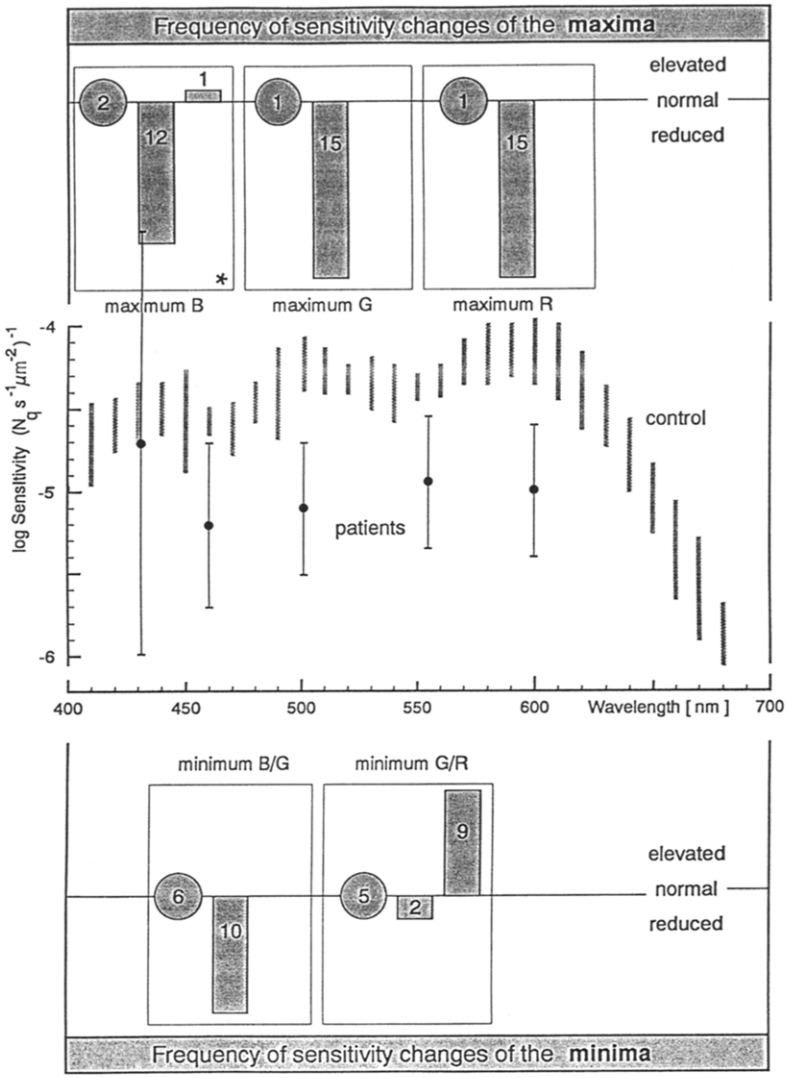

FIGURE 4. The results of the spectral sensitivity measurements of 16 patients suffering from cone dystrophy listed in Tables 4–6 are demonstrated. In the middle panel sensitivity (log *U*) of control (± 1 SD) is plotted against wavelength (nm). Mean and 2 SD of the patients' data are shown by points and vertical bars. The changes in sensitivity of the maxima are demonstrated in the top panel, those of the minima in the bottom panel. Frames and text help to refer to the sections of interpretation among the parts of the figure. The results are expressed in proportion to the size of the bars, their position shows the direction of change (elevated or reduced sensitivity), the number, the frequency of changes found in the patients in the corresponding points of interpretation. Normal results are presented in a circle on the horizontal-zero-line.In most cases the sensitivity of the maxima and the blue/green minima was reduced. A more variable pattern was found for the green/red minimum, where nine patients had an elevated sensitivity.* in one patient sensitivity function could not be measured in the short wavelength region.

For ease of interpretation, the sensitivity of the three maxima (Fig. 4, top), the two minima (Fig. 4, bottom) and the overall sensitivity of the total curve of the patients derived by measuring the peaks of the smoothed function and comparison with the corresponding points of the control curve are shown. A qualitative presentation is given in the figure. It accords with the quantitative evaluation (x, 2 SD) in Table 6.

Figure 4 consists of three parts: in the center of the figure sensitivity in log units (the reciprocal of threshold measured in number of quanta per second and square meters) is plotted against the wavelength (nm) of the visible spectrum. The vertical bars show the control curve obtained by 16 observers (± 1 SD) with its three maxima and the two dips of opponency (minima) between the blue/green and the green/red cone. The points with vertical bars represent the mean and 2 SD of the patients examined at the wavelength of greatest interest (B-, G- and R-Maxima, B/G- and G/R-minima). The data are given in Table 6 together with the data for the control population. Sensitivity can be elevated or reduced in comparison to the control or correspond with it.

Frequency of sensitivity changes of the maxima (Fig. 4, top; and Table 6). The sensitivity of the middle (green) and the long (red) wavelength cones was reduced in all but one of the patients tested. The profile of the short wavelength cone (blue) was more variable. Two patients had a normal blue cone sensitivity and one patient

TABLE 4. Patients suffering from cone dystrophy whose spectral sensitivity was determined

		Blue			Green			Red		
	Patient	n	r	e	n	r	e	n	r	e
1	B.A.		+			+			+	
2	B.M.		+			+			+	
3	B.J.		+			+			+	
4	H.C.		+			+			+	
5	H.G.		+			+			+	
6	I.E.		+			+			+	
7	M.J.		+			+			+	
8	M.P.	+			+				+	
9	P.P.	+				+			+	
10	R.E.		+			+			+	
11	R.S.		+			+			+	
12	R.D.					+			+	
13	R.G.		+			+			+	
14	Sch.H.		+			+			+	
15	Wa.F.		+			+			+	
16	Wa.M.			+		+			+	
		2	12	1	1	15	0	1	15	0

The maxima of the spectral sensitivity curve (B, G, R) are evaluated according to the procedure shown in Fig. 4. The sensitivity for blue, green and red cones in comparison to the control is indicated by n = normal, r = reduced and e = elevated. The bottom line shows the frequency of the sensitivity changes in the patients tested. In most patients the sensitivity for the maxima was reduced in comparison to the control. (The results are demonstrated in Fig. 4, top panel.)

TABLE 5. Patients suffering from cone dystrophy whose spectral sensitivity was measured

		Blue/green			Green/red			Total curve		
	Patient	n	r	e	n	r	e	n	r	e
1	B.A.		+		+				+	
2	B.M.	+					+		+	
3	B.J.	+			+				+	
4	H.C.		+		+				+	
5	H.G.		+			+			+	
6	I.E.		+				+		+	
7	M.J.	+					+		+	
8	M.P.	+					+		+	
9	P.P.		+				+	+		
10	R.E.	+				+			+	
11	R.S.		+				+		+	
12	R.D.		+				+		+	
13	R.G.		+				+		+	
14	Sch.H.		+		+				+	
15	Wa.F.	+			+				+	
16	Wa.M.		+				+	+		
		6	10	0	5	2	9	2	14	0

Here the minima at 490 and 570 nm are evaluated according to Fig. 4 as well as the overall sensitivity (total curve): the sensitivity of the blue/green minimum was reduced, more light was necessary, in 10/16 patients investigated. The sensitivity of the green/red minimum varies more; in most cases the sensitivity is elevated, the dip tends to disappear. As expected, the overall sensitivity for the whole curve was reduced in most cases ($n = 14$). (The results are demonstrated in Fig. 4, bottom panel.)

showed a slight hypersensitivity of the blue cone function, which was never found for the green or red cone function. The hypersensitivity is probably owing to bad fixation, lense opacity or little macular pigment. In most cases, however, (12 of 16 patients tested) the sensitivity of the short wavelength cones was reduced. In one patient no measurement of sensitivity function could be obtained between 400 and 470 nm (see Table 4). Probably this patient can be added to the 12 patients with reduced blue sensitivity. These anomalous single cases of variation in sensitivity are the reason for the large standard deviation.

TABLE 6. Mean and standard deviation values of patients with cone dystrophy in comparison with the control in spectral sensitivity measurement

	Maxima			Minima	
Wavelength [nm]	B 430	G 500	R 600	B/G 460	G/R 560
Control [x]	−4.5	−4.25	−4.1	−4.6	−4.45
[1 SD]	±0.25	±0.25	±0.2	±1.5	±0.2
CD [x]	−4.7	−5.1	−5.0	−5.21	−4.95
($n = 16$) [2 SD]	±1.3	±0.4	±0.4	±0.5	±0.4

B, G and R correspond to the Blue-, Green- and Red- maxima, B/G and G/R to the Blue/Green- and Green/Red- minima.

Frequency of sensitivity changes of the minima (Fig. 4, bottom; and Table 6). The minimum between the middle and the long wavelength cones was more variable, as seen from comparisons between the threshold of sensitivity of the blue/green minimum. In most patients ($n = 9$) sensitivity was elevated, probably due to weakened cone opponency, two patients showed a reduced sensitivity of their green/red minimum and five were within the normal range. The minimum between the short and middle wavelength cones (blue/green) most often showed a decreased sensitivity (10 of 16 tested patients) compared to the control ($n = 6$).

Frequency of sensitivity changes of the total curve (Table 5). As expected the threshold of sensitivity of the whole curve was reduced in almost all patients investigated (14 of 16 patients). Table 4 and Table 5 show the individual data of the patients investigated which are demonstrated in the figure. In two, patient M.P. and P.P., sensitivity of the maxima was not reduced especially the range of the short wavelengths. Both cases were early stages of cone dystrophies. Their condition was diagnosed by means of other tests, i.e., ERG, pattern ERG, etc., and symptoms (visual acuity, glare sensitivity, etc). It can be expected that with progression of the disease the sensitivity of all cones will also decrease. These data show that even in initial stages of the disease, pathological signs can be detected by spectral sensitivity measurements.

Transient tritanopia

Additionally, we tested the interaction of short and long wavelength cones by means of determining transient tritanopia induced by the offset of yellow adaptation light in 13 patients suffering from cone dystrophy. Interpretation and manner of presentation is analogous to the method described for spectral sensitivity measurements; therefore, only the differences shall be mentioned.

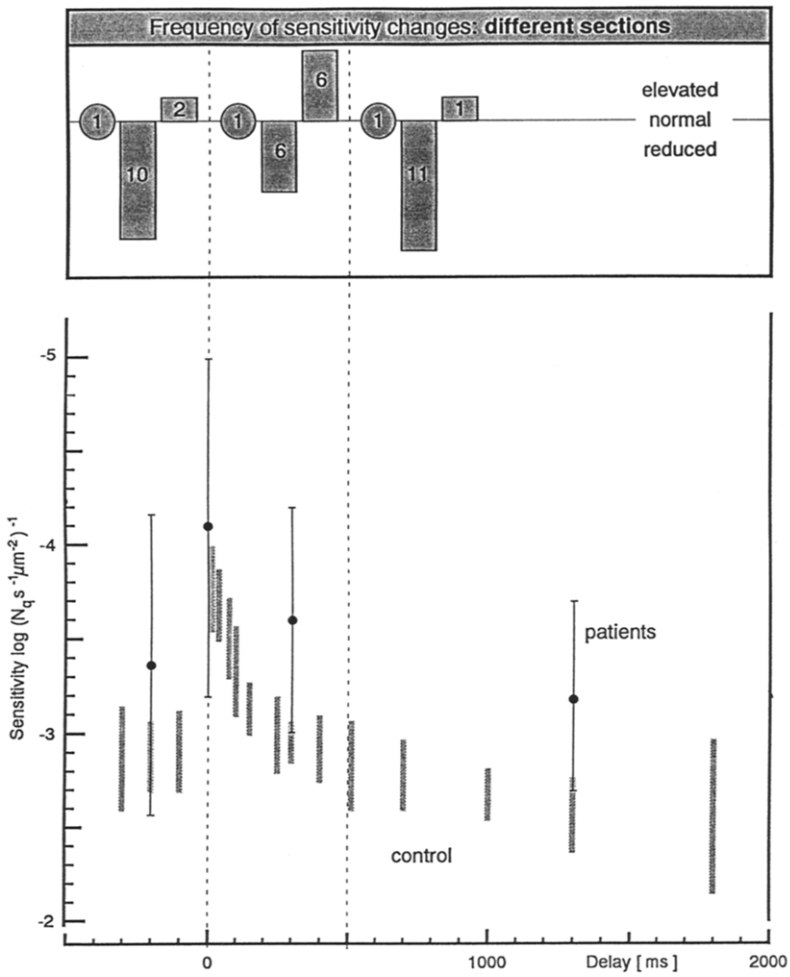

FIGURE 5. Illustration of the results listed in Tables 7 and 8 of the measurement of transient tritanopia of 13 patients with cone dystrophy (see also Fig. 4). Sensitivity (log U) is plotted against time (msec). Mean and standard deviation of the control (gray bars) and cone dystrophy patients (points and vertical bars) are shown in the diagram. Sections 1 and 3 show increased thresholds (= reduced sensitivity) in most cases in comparison to the control curve. The pattern in section 2 is more variable: elevated and reduced thresholds were found with equal distribution ($n = 6$ each).

In the lower part of Fig. 5 the control (± 1 SD, vertical bars) and a representative pathological sample (dotted line) are shown; time (msec) is plotted against the threshold of the blue cones (log U). The vertical dashed lines help to distinguish the different sections 1, 2 and 3 and to identify the corresponding results of our patients illustrated in the upper part of the figure. Section 1 indicates the threshold, which is the reciprocal of sensitivity, in the presence of the adapting light (300, 200 and 100 msec before the extinction of the adapting light). Section 2 represents the initial part of the curve when the test fight is presented to the patient, in the period from 0 to 500 msec after the extinction of the adaptation light. Section 3 is the continuation of section 2; the test light is presented 500–2000 msec after the extinction of the adaptation light.

The graphical arrangement in Fig. 5 is similar to that in Fig. 4. (For explanation see legend of Fig. 4.) Note, in the typical measurement of transient tritanopia the sensitivity scale is inverted. The points of greatest interest chosen for evaluation are those at -200, 0, 300 and 1300 msec. They are shown as points with vertical bars (2 SD) at the relevant time (see Table 8).

The threshold was elevated (and sensitivity reduced) in almost the same quantitative distribution in section 1 (10 patients) and section 3 (11 patients), with one patient having a normal threshold in section 1 and another patient with normal threshold in section 3.

The elevation of the threshold of the blue cones occurring in normals shortly after extinction of the adaptation light (section 2) was found to be reduced and elevated with equal distribution (six patients each); i.e., in six patients the transient reduction of the sensitivity of the blue cones was present, in the other six patients it was reduced or absent.

From these data it becomes clear that cone–cone interaction is pathologic with very variable expression in almost all patients investigated with cone dystrophy.

The results for each patient are given in Table 7. (For interpretation see also Tables 4–6 and Table 8.)

TABLE 7. Results of the measurement of transient tritanopia in patients suffering from cone dystrophy

		−300–0 msec			0–500 msec			500–2000 msec			Total curve		
	Patient	n	r	e	n	r	e	n	r	e	n	r	e
1	B.A.		+				+		+			+	+
2	B.M.		+		+			+			+		
3	H.Ch.		+			+			+			+	
4	H.G.	+					+		+			+	
5	I.E.		+			+			+			+	
6	L.I.		+			+			+			+	
7	M.J.		+			+			+			+	
8	M.P.		+			+			+			+	
9	P.P.			+			+			+		+	+
10	R.S.			+			+		+			+	
11	R.D.		+				+		+			+	
12	Sch.H.		+				+		+			+	
13	Wa.F.		+			+			+			+	
		1	10	2	1	6	6	1	11	1	1	11	1

For interpretation see also Tables 4 and 5. The curve was divided into three different sections and the threshold of the total curve was also compared to the control. The sensitivity was pathologic in all but one case. Reduced and elevated sensitivities are found in equal distribution. The results are demonstrated in Fig. 5.

Dark adaptation

Dark adaptation was tested in 16 patients with cone dystrophy. The threshold of the whole curve, the part of the curve determined by cones (cone threshold), the part of the curve determined by rods (rod threshold) as well as the cone–rod break of the patients were compared with a control group (12 healthy age-matched normals). The results, the control and a pathological sample are shown in Fig. 6, which consists of two parts similar to the construction used in Figs. 4 and 5.

In the lower part of Fig. 6, threshold in log units, as determined by the luminance (cd/m^2) necessary to detect the test spot, is plotted against time of dark adaptation (min). The thick dark line shows the mean while the two thinner lines indicate standard deviation (± 1 SD) of the control sample. An example for a typical pathological curve of a patient with cone dystrophy is shown in symbols connected by lines. The results of the dark adaptation curves of our patients with cone dystrophy are demonstrated in the two blocks in the upper part of the figure. The first block represents the results concerning the cone threshold, the second the results concerning the final rod threshold of the patient curves in comparison to the control.

As shown in the second block of this figure, the final rod threshold itself was normal in all patients. The cone sensitivity was normal in six, and reduced in ten of our investigated patients by more than half a log unit. Usually the cone–rod break was also extinguished.

TABLE 8. Mean and standard deviation values of patients with cone dystrophy compared with the control in transient tritanopia measurement

Time [msec]	−200	0	300	1300
Control [x]	−2.85	−3.8	−2.95	−2.55
[1 SD]	±0.2	±0.3	±0.1	±0.2
CD [x]	−3.35	−4.1	−3.6	−3.2
(n = 13) [2 SD]	±0.8	±0.9	±0.6	±0.5

Values are calculated at the representative times at −200, 0, 300 and 1300 msec.

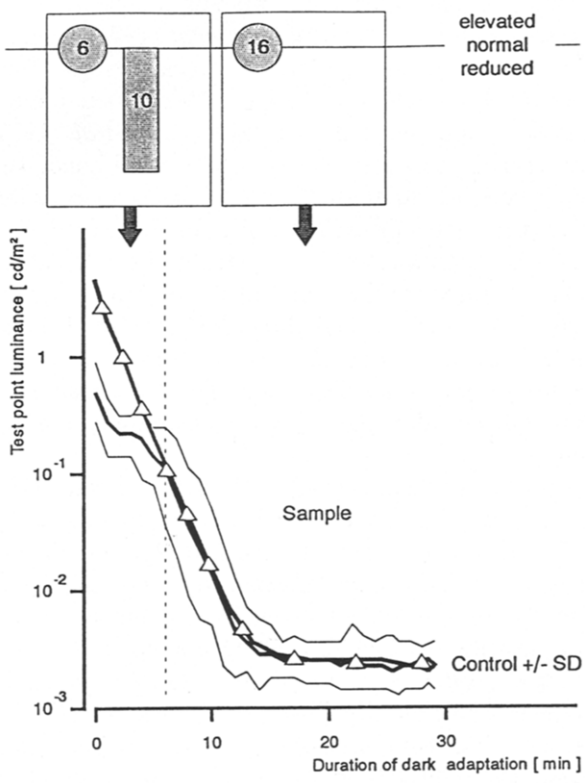

FIGURE 6. Dark adaptation: Time of dark adaptation (min) is plotted against luminance of the test spot (cd/m^2). The vertical dashed line indicates the cone–rod break. The results for the 16 patients with cone dystrophy are shown in the upper part of the figure. (For further details on this type of interpretation see also Figs 4 and 5.) As regards the cone threshold, six patients had a normal dark adaptation curve in the cone branch, 10 patients a reduced sensitivity, none showed an elevated sensitivity. The final rod threshold was normal in all patients tested.

DISCUSSION

Cone degenerations in the initial stages are usually marked by the following symptoms: progressively reduced visual acuity, color vision deficiency and electroretinographic abnormalities, where cone potentials are more affected than rod potentials (Deutman, 1961; Krill *et al.*, 1973; Krill, 1977; Carr & Heckenlively, 1988; Cavender & Everett, 1988; Weleber & Eisner, 1988; Jiménez-Sierra *et al.*, 1989) and often, but not mandatory, mild pigment alterations and reflex abnormalities of the foveal area. In the initial stage ophthalmoscopic alterations are not present or are very mild and the diagnosis has to be based only on case history, psychophysical and electrophysiological test results.

Usually a previously normal patient first notices symptoms in the first to third decade of life (Goodman *et al.*, 1963; Fishman, 1985; Carr & Heckenlively, 1988; Cavender & Everett, 1988; Pagon, 1988; Jiménez-Sierra *et al.*, 1989). Deutman (1961) and Krill (1977) stress, however, that the disease can start at any age of life. According to Krill *et al.* (1973) Krill (1977) and Weleber & Eisner (1988) symptoms do not become as severe and manifest, if the onset occurs later in life. The ages of our patients at the time of investigation were widely spread, but all noticed the first symptoms in the first three decades of their life.

In general, reduced visual acuity, which is noticed by the patient, is one of the first symptoms of cone dystrophy (also see Deutman, 1961; Pearlman *et al.*, 1974; Francois, 1977; Fishman, 1985; Carr & Heckenlively, 1988; Cavender & Everett, 1988; Pagon, 1988). Deterioration is quite variable and can take years (Grey *et al.*, 1977). Final visual acuity after degeneration of all cones very often is near 0.1 (Krill *et al.*, 1973). Visual acuity is then probably mediated by rods as is also found in some of our cases. At approximately this stage glare sensitivity reaches its maximum, because of the missing inhibition of cones on rods in daylight (Alexander & Fishman, 1986). The funduscopic findings also provide a polymorphic picture (Francois *et al.*, 1976; Goodman *et al.*, 1963) and depend on the stage of the disease and the age of onset.

According to Steinmetz *et al.* (1956), Deutman (1961) and Cavender & Everett (1988) we found that the loss of the foveal wall reflex can be the first sign, or, in early stages of the disease, the fundus can be normal or only slightly altered with depigmentations, granular pigmentation near the macula (see also Deutman, 1961; Goodman *et al.*, 1963; Krill *et al.*, 1973; Grey *et al.*, 1977; Cavender & Everett, 1988; Weleber & Eisner, 1988). The typical bull's eye was seen only in the final stages of cone dystrophies (Ullerich *et al.*, 1985). Francois (1977), Fishman (1985) and Carr & Heckenlively (1988) diagnosed an involvement of the peripheral fundus in some cases in the form of pigmentations (Carr & Heckenlively, 1988); also bone spikule-like (Fishman, 1985), or atrophy of choroid and retina (Cavender & Everett, 1988), fundus changes we have observed in mild forms in approximately one-third of our patients. A temporal optic disc pallor may also be evident according to our investigations and other authors (Deutman, 1961; Krill, 1977; Heckenlively, 1982; Fishman, 1985; Cavender & Everett, 1988; Heckenlively, 1988), as well as an attenuation of retinal vessels (Francois, 1977).

Most authors, e.g. Deutman (1961) described a central scotoma, while our results provide a more variable picture. The unexpected concentric constriction observed in some visual fields of the patients investigated is probably due, to a large extent, to the perimetric technique, since the Octopus perimeter involves rod threshold, owing to its dim background illumination. Therefore, slight concomitant rod degenerations show up. Lost fixation is not a criteria for a missing central scotoma in our patients because their fixation was monitored.

Color vision deficiencies were reported by most authors. However, more detailed information about the type of color vision deficiency is rare (Ripps *et al.*, 1987). In accordance with Grey *et al.* (1977) our study shows that color vision deficiency can be evident even if visual acuity of patients with cone dystrophy is normal (Francois *et al.*, 1974). However, with arrangement tests a correlation of color vision defects with visual acuity could be demonstrated. The frequency of severe color vision impairment increases dramatically with reduction of visual acuity to 0.5 and below (see also Krill *et al.*, 1973; Krill, 1977). With progression of cone degeneration (Ullerich *et al.*, 1985; Weleber & Eisner, 1988) color vision tests show a scotopic axis or become erratic (Babel & Stangos, 1973; Krill, 1977; Cavender & Everett, 1988). The error score of the Farnsworth–Munsell 100-hue test and the total color difference score of the saturated Panel D-15 test, provide a good measure of the degree of color vision deficiency.

Our measurements of cone spectral sensitivity allowed a more detailed study of the behaviour of short, middle and long wavelength cones. A reduction in sensitivity was found for all cone mechanisms, but was most obvious for the middle and long wavelength cones. Consequently the threshold of the complete function was elevated, which is in contrast to the forms of selective cone dystrophies, where only one type of cone degenerates (Sadowski & Zrenner, 1994; Kellner *et al.*, 1995). Spectral sensitivity measurements in enhanced S cone sensitivity syndrome, for example, are mediated by the short wavelength-sensitive cones (Kellner *et al.*, 1993). In our patients, however, a difference in the threshold of the two minima that reflect strength of opponency was evident. The dip in blue/green spectral opponency tends to show elevated thresholds similar to the maxima, whereas the dip of opponency between the middle and long wavelength sensitive cones near 560 nm tends to disappear. This major loss of opponency and fusion of R/G cone signals with resulting disappearance or even inversion of the dip at 560 nm has been described so far in one case with cone dystrophy (Zrenner *et al.*, 1986b; Klingaman & Baier, 1989). Our observations confirm this

finding as a regular pathophysiological process in cone degeneration.

The magnitudes of the minima indicate the strength of opponency between the antagonistic mechanisms of cones (Zrenner, 1982, 1983). In normal trichromats the short wavelength sensitivity is controlled in part by the action of the long wavelength cone (Mollon & Polden, 1979; Zrenner, 1982, 1983). The blue cone sensitivity maximum can be reduced while the opponency between short- and long wavelength cones is still functioning. On the other hand, there were fewer patients with sensitivity reduction of the blue cone maximum than those with sensitivity reduction of the R/G maxima. This might explain the lack of uniformity of the results obtained in the test of transient tritanopia.

Despite the well maintained blue cone function, tritan defects are more frequent than protan or deutan defects in advanced stages. This may have its origin in the particular distribution of blue cones (Marc & Sperling, 1977) as well in their generally low number (Zrenner *et al.*, 1990).

An abnormality of the cone dark adaptation function was found in 10 of 16 tested patients. This corresponds to previous reports, where cone function was reduced in most patients, while the scotopic part was not altered (Deutman, 1961; Goodman *et al.*, 1963; Babel & Stangos, 1973; Krill *et al.*, 1973; Francois, 1977; Berson *et al.*, 1968; Ripps *et al.*, 1987; Weleber & Eisner, 1988). Owing to the elevated cone threshold the dark adaptation curve becomes monophasic (Sloan & Brown, 1962). In the initial stage of hereditary cone dystrophies all results of ophthalmological and psychophysical tests are highly variable (also see Krill *et al.*, 1973). The disease has a very polymorphic appearance. With progression of the disease, symptoms become more evident. Finally, the symptoms of the disease become more univariant in the patients when all cones are degenerated and visual function is maintained only by rods.

Only in this stage are the bull's eye, monochromatic color vision and disturbed cone–cone and cone–rod interaction with absent transient tritanopia, a high glare sensitivity, visual acuity of 0.1, monophasic dark adaptation curve and central scotoma, detectable also by routine methods, found.

The rod system was not involved in most of our patients, but the possibility that its degeneration will follow cone degeneration cannot be dismissed.

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