Bull's eye maculopathy with early cone degeneration

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SUMMARY Seven patients with acquired cone degeneration were investigated. The initial visual acuities in 6 of the series were normal or near normal but later deteriorated, although they did not fall below 6/60 in any patient. All the patients tested had colour vision defects and abnormalities on electrodiagnostic testing referable to the cone system. The typical picture was of a bull's eye maculopathy accompanied by an annular scotoma around the fovea, but the clinical and electrophysiological investigations showed that there were considerable variations especially in the early stages.

Bull's eye maculopathy has a characteristic appearance; there is a dark central area at the fovea with a paler zone around it. Round the pale area there is frequently a hyperpigmented ring. The changes are nearly always bilateral and appear symmetrical. This abnormality of the macula can be caused by several disorders of the retina and pigment epithelium. Drug toxicity, the cone dystrophies, central serous retinopathy, senile predisciform macular degeneration, dominant macular dystrophy, fundus flavimaculatus, and Batten Mayou disease have all been described with this appearance (Weise and Yannuzzi, 1974; Deutman, 1974; Kearns and Hollenhorst, 1966).

The acquired cone dystrophies are recognised by the triad of signs: diminished visual acuity, diminished colour vision, and abnormalities of the photopic portion of the electroretinogram (Goodman *et al.*, 1963; Krill, 1966; Krill and Fishman, 1971; Kelsey and Arden, 1972). In cases of acquired cone dystrophy a bull's eye degeneration of the macula is a well-recognised feature (Sloan and Brown, 1962; François, 1974) although the fundus may appear either normal or with pigment granularity of the macula or with choroidal atrophy (Steinmetz *et al.*, 1956; Babel and Stangos, 1972; Krill *et al.*, 1973; Ohba, 1974).

The present series of patients, with one exception, attended early in the course of their disease and, when they were symptomatically only mildly affected, showed various features which may be misleading in making the diagnosis. They were investigated and assessed to see whether a common pattern and disease entity could be found.

Patients and methods

The 7 patients in this series presented to Moorfields Eye Hospital for further investigation of failing vision. They were referred to the retinal diagnostic department between 1969 and 1975 either by outside ophthalmologists or by other consultants on the staff at Moorfields.

With the exception of Case 4, who had an affected relative, the patients all had a bull's eye appearance of their maculae similar to that already described.

They were investigated further with refraction, visual field testing, colour vision assessment, electrodiagnostic studies, and colour and fluorescein photography.

Field charting was performed on a Bjerrum screen with either 1/1000 or 2/1000 test objects. Initially, Goldmann perimeter fields were also attempted, but it was found that with some patients with a small central island of sparing the test object disappeared in the central fixation spot. With the Bjerrum screen the patients had no difficulty with fixation owing to their 'tunnel' vision, and were easily able to see the test object close to the central fixation spot.

Colour vision was assessed with Hardy Rand Rittler isochromatic plates under standard illumination. Farnsworth Munsell 100 hue testing was also attempted on 5 patients, but on only 1 was a reliable test obtained. Two patients had visual acuities which precluded 100 hue testing, and the other 2 patients had such poor colour vision they were incapable of performing the test.

Colour photography was performed with a Carl Zeiss Jena (Retinophot) camera using Kodak Ektachrome X film (ASA 64). Fluorescein angiography was carried out by injection of 5 ml of 20%

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sodium fluorescein into an antecubital vein. The photographs were taken on a West German Zeiss fundus camera using Ilford FP4 film (ASA 125). The excitatory filter was a Baird atomic B5 and the barrier filter an Ilford 109.

Electrodiagnostic tests were performed on all patients. These included an electro-oculogram (EOG), photopic and scotopic electroretinogram (ERG), and critical fusion frequencies (CFF). A flash visually evoked response (VER) was performed on 2 patients and a pattern VER on 5 patients.

The EOG was carried out as described by Arden *et al.* (1962). 30 degree eye movements were made between fixation lights, and the electrical potentials were recorded on a Medelec MS6 machine.

The ERG technique was based on that used by Karpe (1945). A haptic contact lens was used with the electrode and the pupil was dilated. The light source was a xenon stroboscope.

The visually evoked responses were recorded either on a Medelec MS6 or computer of average transients. The stimuli in some cases were flashes of light and in others were reversing checkerboard patterns. The checkerboard patterns varied in size from 11.5' arc to 46' arc and in contrast from 20 to 50%. The reversals were mostly at 10 Hz but some patients were tested with 2 Hz.

Follow-up on the patients varied from 6 months to 7 years. One patient was seen on only 1 occasion as she then returned home overseas.

Case Histories

CASE 1

A 35-year-old white man presented to the hospital in 1969 with defective vision and mild photophobia. Six years previously he had 6/6 vision in each eye with a myopic correction. *Visual acuity*: 6/24 right, 6/9 left. *Fundi*: typical bull's eye appearance of the maculae (Fig. 1). *Fields*: central scotoma in each eye; no central island of sparing was demonstrated. *Fluorescein angiography*: bilateral hyperfluorescent oval ring from the intact choriocapillaris underlying the pale area of pigment epithelium (Fig. 1). *Heredity*: his parents had good vision with suitable glasses; he had no siblings. His 4 children had normal visual acuities, colour vision to HRR plates, and ophthalmoscopically normal fundi.

Follow-up: 5 years later he was reassessed and further investigated. *Visual acuities*: 6/60 right and left. *Fundi*: increase in size of the bull's eye (Fig. 1). *Colour vision*: HRR—marked protan, deutan, and tritan defect. 100 hue—not possible. *Fluorescein angiography*: increase in the area and density of the transmission defect (Fig. 1). *Electrodiagnostic tests*:

EOG: 213% right, 240% left. ERG: reduced photopic b-wave right and left. CFF: >60 right and left. VER: (2 Hz, 20% contrast, 46' arc squares) markedly reduced amplitudes with normal conduction times.

CASE 2

A 28-year-old white man had been noted in 1969 to have very poor colour vision, but no other ocular abnormality was detected. He presented in 1971 complaining of loss of vision, especially when watching a moving ball. His general health was good although he had suffered a bout of malaria in 1970. For this he was treated with chloroquine sulphate 200 mg weekly for 6 months (i.e., a total dose of chloroquine of approximately 5 g), and he was then treated with pyrimethamine 25 mg weekly, which was continued prophylactically. *Visual acuities*: 6/9 in each eye with myopic correction. *Fundi*: normal. *Fields*: ring scotoma around central fixation from 2° to 4° (Fig. 2). *Colour vision*: HRR plates showed severe red-green and moderate blue-yellow defects. *Fluorescein angiography*: normal. *Electrodiagnostic tests*: EOG: within normal limits—right 223% and left 181%. ERG: scotopic ERG: normal photopic ERG: reduced b-wave. CFF: 40 right and left. VER: (10 Hz 23' arc squares, 20% contrast) grossly reduced amplitudes. *Heredity*: there was no family history of poor central vision.

Follow-up: three years later he was reviewed. *Visual acuities*: 6/18 right and 6/24 left. *Fundi*: right normal; left bull's eye maculopathy. *Fields*: unchanged. *Fluorescein angiography*: bilateral pigment epithelial transmission defects (Fig. 3).

CASE 3

A 37-year-old white man was diagnosed in October 1971 in another ophthalmic unit as having macular degeneration. His vision was 6/9 right, 6/6 left with paracentral scotomata. He was first seen in Moorfields Eye Hospital in March 1973. *Visual acuities*: 6/12 right, 6/6 left, with myopic correction. *Fundi*: typical bull's eye appearance in both eyes (Fig. 4). *Fields*: (Goldmann perimetry) bilateral scotomata of the central 5°. *Colour vision*: HRR plates: mild red-green defect. Farnsworth Munsell 100 hue test: tritan defect in the right eye with a suggestion of a similar defect in the left eye (Fig. 5). *Fluorescein angiography*: annulus of transmission defect around the fovea (Fig. 4). *Electrodiagnostic tests*: EOG: 170% right and left. *Heredity*: this patient had a dominant family history of macular disease. His mother and aunt had been known to have macular degeneration since an early age; unfortunately, they could not be investigated. His brother also had macular degeneration from an early age and is

Fig. 1 Case 1. (a): Fundus photograph of right eye December 1970 with typical bull's eye lesion of macula. (b): Fluorescein angiogram at same date as (a) with annulus of pigment epithelial atrophy corresponding to the pale area in (a). (c): Fundus photograph January 1976; the area of the bull's eye has increased. (d): Fluorescein angiogram on same date as (c); pigment epithelial atrophy has increased similarly

reported as Case 4 in this series. He had 2 children—an 11-year-old son with normal visual acuities, fundi, colour vision, and electrodiagnostic tests, and a 7-year-old daughter with normal acuities and colour vision but her fundi had mild granularity of the pigment epithelium at the foveae.

Follow-up: 2 years later. *Visual acuities:* 6/12, 6/9. *Fundi:* no change. *Fields:* annular defect from

1° to 5° around central fixation. *Colour vision:* HRR unchanged. 100 hue showed deterioration in left eye (Fig. 5). *Fluorescein angiography:* unchanged. *Electrodiagnostic tests:* EOG: 184% right and left. ERG: photopic and scotopic normal. CFF: 80 right and left. VER: flash: low amplitudes recorded with delay of 220–250 ms pattern: (10 Hz, 50% contrast, 46' arc squares) minimal responses.

Fig. 2 Case 2: typical ring scotomata with 1/1000 white objects corresponding to the area of pigment epithelial atrophy in Fig. 3

CASE 4

A 46-year-old white man, and brother of Case 3, had gradual deterioration of vision over 3 years from the age of 12. *Visual acuities*: 6/60 in each eye with glasses. *Fundi*: well-defined circular area of atrophy of the pigment epithelium underlying both maculae with surrounding multiple, small, white patches in the pigment epithelium (Fig. 6). The central defect was similar to central areolar choroidal sclerosis, although the underlying larger vessels appeared normal. *Fields*: central scotoma in each eye with no central sparing. *Fluorescein angiography*: confirmed the absence of pigment epithelium centrally with atrophy of the choriocapillaries. There were multiple transmission defects corresponding to the small white patches (Fig. 6), but the

larger flecks had hypofluorescent centres throughout the angiogram. *Electrodiagnostic tests*: EOG: was reduced 160% right and 155% left. VER: mild reduction in amplitude with normal conduction times to flash stimulus. *Heredity* see Case 3. He had no children.

Follow-up: no follow-up examination was performed on this patient as his disease had been static for 30 years.

CASE 5

A 24-year-old white woman attended her local ophthalmologist in January 1973 complaining of blurred vision in both eyes. Her visual acuities were 6/12 right, 6/6 left with a small myopic correction, and her maculae were seen to have a granular

Fig. 3 Case 2: fluorescein angiogram showing oval area of pigment epithelial atrophy in both eyes

Fig. 4 Case 3 (a): Fundus photograph right eye May 1973: typical bull's eye maculopathy. (b): Fluorescein angiogram same date as (a); annular transmission defect of pigment epithelium. (c) and (d): Fundus photograph and fluorescein angiogram May 1975 showing no increase in size of affected area

appearance. A year later her visual acuities were 6/12 right and 6/9 left, and Bjerrum field charting showed a paracentral scotoma in the right eye and an annular defect in the left eye (Fig. 8). She was referred to Moorfields for further investigation. *Visual acuities*: 6/12 right, 6/9 left. *Fundi*: dark central area at the fovea with a perifoveal granular ring of pigment epithelial change. Around this ring

was a band of normal looking retina, then a further ring of white flecks in the pigment epithelium (Fig. 7). *Fields*: annular defects right and left (Fig. 8). *Fluorescein angiography*: a hypofluorescent zone centrally with surrounding patches of transmission defect (Fig. 7). The white pigment epithelial lesions were hyperfluorescent and faded as the eye transit progressed. A few larger flecks had hypo-

Fig. 5 Case 3. 100 hue charts of both eyes. (a) and (b): May 1973. (c) and (d): May 1975. There is a mild increase in the tritan defect of both eyes

fluorescent centres throughout the angiogram. *Heredity*: there was no family history of visual disturbance. Her parents had normal vision; she had no siblings.

Follow-up: one year later she was reviewed. *Visual acuities*: 6/12 right; 6/24 left. *Fundi*: unchanged. *Fields*: further extension of ring scotomata (Fig. 8). *Colour vision*: HRR: almost achro-

matopsic. 100 hue: incapable of performing the test. *Electrodiagnostic tests*: EOG: 155% right and left. ERG: photopic reduced b-wave. scotopic normal. CFF: 16 right and left. VER: (10 Hz 20% contrast 23' arc squares) extremely low amplitudes.

CASE 6

A 28-year-old white man was seen in February 1974

Fig. 6 Case 4. (a) and (b): Fundus photographs of both eyes showed extensive pigment epithelial atrophy with visible large choroidal vessels. Note the white flecks at the level of the pigment epithelium (arrows). (c) and (d): Fluorescein angiograms of the lesions in (a) and (b) with loss of the choriocapillaris. The larger pigment epithelial flecks have hypofluorescent centres (arrows)

with gradual loss of vision during the previous year. Prior to this he had 6/9 in both eyes with myopic glasses. *Visual acuities*: 6/18 right, 6/24 left. *Fundi*: typical bull's eye maculae (Fig. 9). *Fields*: bilateral paracentral scotomata; the field defect in the right eye was confined above the horizontal but in the left eye it extended downwards in a horseshoe

pattern (Fig. 10). *Colour vision*: HRR plates showed a severe red-green deficiency and moderate blue-yellow deficiency: FM 100 hue testing was not possible. *Fluorescein angiography*: annular transmission defect in both eyes (Fig. 9). *Electrodiagnostic tests*: EOG: right 160%, left 190%. ERG: photopic reduced b-wave left eye; scotopic normal.

Fig. 7 Case 5. (a) and (b): Atypical bull's eye maculopathy of both eyes with patchy pigment epithelial atrophy and white flecks in the pigment epithelium. (c) and (d): Fluorescein angiograms of (a) and (b): the larger flecks have hypofluorescent centres

CFF: 60 right and left. VER: (46' arc 20% contrast, 10 Hz) unrecordable in right eye and very small amplitudes in left eye (11.5' arc 20% contrast, 10 Hz) amplitudes in both eyes rose to 1.2 μ v. *Heredity*: there was no family history of poor vision. His 2 sisters had normal acuities, colour vision, fundi, and fluorescein angiograms.

Follow-up: 12 months later he was reviewed.

Visual acuities: 6/36 right, 6/60 left. *Fundi*: unchanged. *Fluorescein angiography*: unchanged.

CASE 7

A 23-year-old white woman in 1972 noticed difficulty playing tennis, as the ball disappeared when she was about to hit it. In October 1972 she was examined locally but no ocular defect was seen. Her

Fig. 8 Case 5: serial fields of both eyes with 1/1000 white objects showing marked deterioration. There was little change in the visual acuities over the same period

vision gradually deteriorated, and she was referred for further investigation in March 1974. *Visual acuities*: 6/9 in each eye. There was no refractive error. *Fundi*: typical bull's eye appearance (Fig. 11). *Fields*: annular defect from 1° to 4° from the fovea. *Colour vision*: HRR plates: mild red-green defect. *Fluorescein angiography*: annular transmission defect around the fovea (Fig. 11). *Electrodiagnostic tests*: EOG: 186% right, 190% left. ERG: photopic low amplitude b-waves in both eyes; scotopic normal.

CFF: 40 right, 60 left. *Heredity*: she had no siblings; her parents had normal acuities and fundi.

Follow-up: the patient returned to Argentina, and further follow-up studies were not possible.

Results

The results are summarised in Table 1.

VISUAL ACUITY

All the patients studied except Case 4 had normal or

Fig. 9 Case 6. (a) and (b): Fundus photographs of both eyes with typical bull's eye maculopathy. (c) and (d): Fluorescein angiograms of the same areas as (a) and (b) with hyperfluorescence corresponding closely to the pigment epithelial pallor

near normal acuities when first seen. They showed deterioration of visual acuity during the period of follow-up, though the rate of visual loss was variable (Table 1). Case 3 showed minimal change over 3 years, whereas Case 6 had considerable worsening of acuity over 1 year. The remaining patients ranged between these extremes, although no follow-up was possible on Case 7.

The 2 patients with long-standing disease both had acuities of 6/60 but were able to carry out their occupations without difficulty. No patient had vision worse than 6/60 in either eye and some patients showed a moderate degree of asymmetry in the acuities of each eye.

Apart from Case 7 all the patients were myopic, although the greatest refractive error was -7.00

Fig. 10 Case 6: paracentral scotomata in both eyes to 1/1000 white test objects

dioptries, and none showed other signs of degenerative changes associated with myopia, nor did the degree of myopia change appreciably.

COLOUR VISION

Colour vision defects were present in all patients tested (Table 1). The Hardy Rand Rittler plates showed 3 patients to be almost achromatopsic, 1 patient to have severe red-green with moderate blue-yellow deficiency, and 2 patients with mild red-green deficiency. Only in 1 of these last patients (Case 3) was a Farnsworth Munsell 100 hue test possible. This produced a result indicative of a tritan defect rather than the protan or deutan defect suggested by the HRR plates. One patient with good visual acuity was not tested with the 100 hue test, but the remaining patients with a visual acuity good enough to perform the test found it impossible to carry out in any meaningful way as their hue discrimination was inadequate.

VISUAL FIELDS

The typical field defect found in these patients was a ring scotoma around central fixation. It extended from 1° out to 5° from the fovea and corresponded closely to the area of pigment epithelial change visible in the fundus. Cases 1 and 4, in whom the disease was longstanding, did not show these changes. Their visual acuities had fallen to 6/60 in each eye and a central area of sparing could not be demonstrated when specifically looked for. Case 6, who was also severely affected, did not have a ring scotoma. Both eyes had an upper paracentral defect, and in the left eye this extended down as if developing into an annular defect (Fig. 10).

Cases 2 and 3 had ring scotomata which remained static over the period of examination. Case 5 showed a progression of the ring scotoma (Fig. 8). During a 10-month period her visual acuity remained static at 6/12 in her right eye, although the field deteriorated.

Her left eye showed a deterioration in both acuity and field.

No peripheral field defect was detected in any of the patients.

FUNDAL APPEARANCE

Five out of the 7 patients studied had similar fundal appearances with a normal or slightly darker than normal small central area surrounded by a lighter band. Around this lighter band was a further thin dark rim.

Two patients had atypical fundal lesions. Case 5 had a pigmented ring close to the fovea and white flecks in the pigment epithelium around the periphery of the macular area. Case 4 had a markedly different picture with an area similar to central areolar choroidal sclerosis at the fovea but white flecks in the pigment epithelium of the posterior pole similar to Case 5. During the period of observation the lesions appeared on ophthalmoscopy to change little, though the bull's eyes of Case 1 enlarged and Case 2 developed bull's eye lesions after 3 years.

FLUORESCIN ANGIOGRAPHY

Fluorescein angiograms of the typical bull's eye lesions all showed a ring of hyperfluorescence corresponding closely to the paler zone on ophthalmoscopy. Of the 4 patients with serial angiograms 2 showed no appreciable change in the size of the lesions, 1 developed lesions during the period of observation, and the fourth showed a definite increase in the area involved and density of hyperfluorescence (Fig. 1). One patient showed typical transmission defects but had no serial photographs.

The 2 patients with atypical fundi showed other features. Case 5 showed pigment epithelial atrophy which was patchy over a large part of the macular area with a central hypofluorescent area. The large flecks visible on ophthalmoscopy were hypofluorescent centrally with hyperfluorescence at the

Fig. 11 Case 7. (a) and (b): Fundus photographs with typical bull's eye maculae. (c) and (d): Fluorescein angiograms with annular transmission defects from the pigment epithelial atrophy

edges. The small flecks were hyperfluorescent, with no central masking of the fluorescein. The appearance of the flecks changed little during the course of the angiogram but faded gradually as the background fluorescence faded.

Case 4 had marked loss of the central pigment epithelium and underlying choriocapillaris (Fig. 6). The larger choroidal vessels filled normally and did

not appear to be grossly different from central areolar choroidal sclerosis. The white flecks in the pigment epithelium had the same characteristics as those in Case 5.

ELECTRODIAGNOSTIC TESTS

Electro-oculogram

The EOG was normal in all the patients with a

Table 1

Case	Age	Sex	Refraction	VA first recorded	VA final	Colour vision	Field	Fundus
1	35	M	R: -4.00/-3.00 L: -3.75/-2.00	R: 6/6 L: 6/6	R: 6/60 L: 6/60	Achromat	Central scotoma	BE
2	28	M	R: -1.50 DS L: -1.50 DS	R: 6/9 L: 6/9	R: 6/18 L: 6/24	Strong R-G and moderate B-Y defects	Ring scotoma 2°-4°	N
3	37	M	R: -4.00/-0.75 L: -4.00/-0.75	R: 6/9 L: 6/6	R: 6/12 L: 6/9	Mild R-G and ? B-Y defects	Ring scotoma 1°-5°	BE
4	46	M	R: -2.00/-1.00 L: -1.50 DS	R: 6/60 L: 6/60	R: 6/60 L: 6/60	ND	Central scotoma	Choroidal atrophy with PE flecks
5	25	F	R: -0.50 L: -0.50	R: 6/12 L: 6/6	R: 6/12 L: 6/24	Achromat	Paracentral scotoma/ Ring scotoma	A typical BE with PE flecks
6	28	M	R: -2.75/-2.50 L: -3.50/-0.75	R: 6/9 L: 6/9	R: 6/24 L: 6/60	Achromat	Paracentral scotoma	BE
7	22	F	R: Emmetropic L: Emmetropic	R: 6/9 L: 6/9	—	Mild R-G defect	Ring scotoma 1°-4°	BE

BE=Bulls eye. D=Dominant. ND=Not done. R-G=Red/green. SN=Subnormal. B-Y=Blue/yellow.

typical bull's eye fundus. The two atypical patients with flecks had an EOG moderately reduced to 155-160% light rise.

Electroretinogram

The scotopic ERG was normal in all patients.

The photopic ERG had a reduced b-wave in all the patients tested apart from Case 3, who was the most mildly affected patient in the series. The a-waves were unaffected even in those patients who had had the disease many years.

Critical fusion frequency

The CFF showed a more variable pattern. Three patients had a normal CFF in both eyes and another patient had a normal CFF in 1 eye. Case 5, with the atypical fundal appearance, had a CFF of 16 in each eye. Case 2 had a CFF of 40 in each eye at a time when his fundi appeared normal, although his vision later deteriorated to 6/18 right, 6/24 left.

Visually evoked response

The pattern VER showed a severe reduction in the amplitude of the wave recordings in all the patients tested. Case 6 was found to have higher amplitudes when the square size was reduced from 46' arc to 11.5' arc, though they still remained very low. The increased number of edges from the smaller squares which crossed the centrally spared area of the macula would account for this heightened response. Two patients had a flash VER. Case 3 had reduced amplitudes and a marked delay in the conduction time to the cortex (220 ms right eye and 250 ms left eye). This could not be explained, especially as

he was the least severely affected patient in the series. Case 4 had mildly reduced amplitudes. Case 5, with the atypical bull's eye lesions, showed a reduced response, but when only the central areas were tested the amplitudes fell to unrecordable levels.

GENETICS

Two patients had dominant inheritance with very different clinical and electrophysiological manifestations. Case 3 had bull's eyes maculae with mild colour and electrophysiological disturbances, whereas Case 4 had marked macular atrophy.

Although there was no history of consanguinity, the remaining patients were considered to be either recessive or sporadic cases. No affected relatives were found and there was no family history of visual loss. Within this group of 5 patients the progress of the cone loss was very variable; 1 had a slow deterioration over 13 years, 1 had a gradual loss over 3 years, and 2 had more rapid involvement over 1 to 2 years.

Discussion

VISION

Visual acuity

The majority of the patients form a distinct entity with a presenting symptom of visual loss, although the visual acuity may be normal or near normal on testing with a Snellen chart. Later the central vision may be reduced to 6/60, but this is not invariable, and deterioration may take many years.

Most published series of cone degeneration do not have follow-up information, but the results here

Fluorescein angiography	EOG	Photopic ERG	Scotopic ERG	CFF	VER	H	Follow-up	Progress
Ring transmission	N	SN b-wave	N	N	Low ampl.	R/S	Increase in size of BE (Fig. 1)	Slow deterioration over 13 years
N	N	SN b-wave	N	Reduced	Low ampl.	R/S	Developed BE lesion (Fig. 2)	Moderate deterioration over 3 years
Ring transmission	N	N	N	N	Low ampl. delayed	D	Mild colour deterioration 100 hue (Fig. 5)	Mild deterioration over 3 years
Atrophy of chorio-capillaris	SN	ND	ND	ND	Low ampl.	D	Static	Severe deterioration many years previously
Patchy transmission								
Central hypo-fluorescence	SN	SN b-wave	N	Very reduced	Low ampl.	R/S	Increase in area of field loss (Fig. 8)	Moderate loss over 1 year
Patchy transmission								
Ring transmission	R: SN L: N	R: N L: Sl. SN b-wave	N	N	Low ampl.	R/S	No apparent change in retinae	Severe deterioration over 2 years
Ring transmission	N	Sl. SN b-wave	N	R: reduced L: N	ND	R/S	No follow-up	No follow-up

N=Normal. PE=Pigment epithelium. R/S=Recessive/sporadic. H=Inheritance

broadly agree with those of Krill *et al.* (1973), although they had no case of bull's eye maculopathy with vision better than 6/12. They found that the rate of visual loss varied greatly from patient to patient and that the final acuity often remained at 6/60. There was also a moderate degree of asymmetry between the acuities of the 2 eyes as found with this series. They also suggested that younger patients tend to be more severely affected than those in whom the disease becomes manifest later in life. This idea would be borne out by this series, though all the patients developed symptoms between the ages of 22 and 35 years apart from Case 4. He was affected at the age of 12 and showed greater macular atrophy than the others. It is interesting that his brother did not have symptoms until the age of 35, and he was less affected than the other patients. They presumably had a dominantly inherited disease, but their clinical appearances and visual functions were very different.

None of the patients had nystagmus, and only 1 patient had symptoms of photophobia. Both nystagmus and photophobia are well recognised accompaniments of cone disfunction although by no means consistently found (Goodman *et al.*, 1963; Kelsey and Arden, 1972).

Colour vision

In degenerative conditions of the cone photoreceptors abnormalities of colour vision are usually present and invariably so in the cone disfunctions. Few of the patients in this series were initially aware of this abnormality until tested. However, in Case 2 colour loss was his original symptom and it pre-

ceded any loss of visual acuity or visual field by 2 to 3 years. Previously reported series in which colour vision has been assessed do not seem to have had similar difficulty with the 100 hue test as experienced by us. Even though the acuities of some of our patients were good their colour vision was severely affected as shown by the relatively crude HRR plates.

Visual fields

An annular field defect was demonstrated in 4 patients and paracentral scotomata were found in another. It is conceivable that the remaining 2 patients may have had similar field defects if they had been seen earlier in the course of their disease and they had been specifically looked for.

Annular field defects have been noted previously with cone dystrophies (Sloan and Brown, 1962; Krill *et al.*, 1973; Yokoyama *et al.*, 1974), and resemble those of chloroquine retinopathy (Okun *et al.*, 1963; Kearns and Hollenhorst, 1966). Sparing of the foveal cones with preservation of good visual acuity and more severe loss of perifoveal cones could account for the ring field defect. Goodman *et al.* (1963) found no demonstrable field defect in the majority of their patients tested, but only one had a bull's eye macula.

RETINAL MORPHOLOGY

The typical fundus appearance of a bull's eye pigmentary abnormality with a corresponding ring transmission defect on fluorescein angiography was present in 5 of the patients. This appearance resembles chloroquine retinopathy but is usually

more localised. Chloroquine toxicity is the most widely recognised cause of bull's eye maculopathy, and cases have been described with annular field defects and sparing of the central vision (Okun *et al.*, 1963; Kearns and Hollenhorst, 1966). However, chloroquine retinopathy does not produce a specific b-wave loss in the ERG, and both the ERG and EOG may be affected independently. The bull's eye itself is often larger with more diffuse changes in the pigment epithelium on fluorescein angiography. Siegel and Smith (1967) described a case of non-progressive bull's eye maculopathy and ring scotoma following drug toxicity which was not due to chloroquine, but most other toxic retinopathies do not produce a bull's eye lesion. Case 2 had received chloroquine for malaria but the total dose (5 g) was well below that normally associated with macular degeneration and his colour vision loss preceded the onset of malaria.

Other causes of bull's eye maculopathy are less common. Weise and Yannuzzi (1974) reported 9 patients who had annular transmission defects on fluorescein angiography. Although they did not perform colour vision testing or electrodiagnostic studies, their cases included central serous retinopathy, fundus flavimaculatus, Stargardt's juvenile macular degeneration, and senile predisciform changes of the pigment epithelium.

Chopdar (1976) described a case of bull's eye maculopathy in a woman with peripheral vascular closure of the retina. He did not link the 2 abnormalities, and the electrophysiology and colour vision showed the macular changes were not due to cone dysfunction.

ELECTROPHYSIOLOGY

The normal scotopic ERG indicated that either the abnormality was confined to the cones or that the macular area only was involved (Merin and Auerbach, 1970). On electrodiagnostic testing the loss of the photopic b-wave and markedly diminished VER appeared to be a consistent finding. The ERG abnormalities suggested widespread cone loss and that the rods were intact. Sparing of the a-wave and involvement of the b-wave is difficult to explain, although it has been noted previously by Yokoyama *et al.* (1974). Although a normal photopic ERG is against the diagnosis of cone dysfunction, Case 3 had the other criteria of this disorder and had affected relatives. Four of the 24 bull's eye patients of Krill also had normal photopic electro-retinograms.

The photopic ERG and CFF indicate the degree of cone involvement in the whole retina, but it may be from these results that the photopic ERG is a more sensitive indicator of cone abnormality in this disorder than CFF levels.

Cases 4 and 5 had a more generalised pigment epithelial disease than the other 5 patients, which accounts for the flecks and reduced EOG. Krill *et al.* (1973) found a reduced EOG in 12 of their 24 patients with a bull's eye appearance and cone dystrophy, and Kelsey and Arden (1972) found an abnormal EOG in 9 of their 13 patients with cone dysfunction.

Abnormalities of the VER have not been described previously in cone dysfunction in any detail, presumably because the macular involvement has been assumed always to affect the response. In this series the degree of involvement seemed out of proportion to the loss of foveal cones, as 4 of the patients had 6/9 vision or better in at least 1 eye when tested. The pattern VER, which reflects the macular function, would be expected to have near normal amplitudes with good visual acuity. The reduced flash VER response was a further indication of the generalised nature of the receptor dystrophy.

GENETICS

Dominant, recessive, and X-linked inheritance have been described with acquired cone dystrophies (Goodman *et al.*, 1963; Berson *et al.*, 1968a; Davis and Hollenhorst, 1955; Krill and Deutman, 1972; Pearlman *et al.*, 1974). None of our patients showed X-linked inheritance, which according to Goodman *et al.* (1963), tends to be manifest in children and become static early in life.

The 2 related patients had dominant inheritance and showed markedly different fundal pictures. Such a degree of variation is unusual, although Steinmetz *et al.* (1956) examined a dominant family of 158 members and found that one branch developed pigment granularity of the fovea and another branch developed choroidal atrophy. Similar disparity was also previously noted with dominant inheritance in cone dystrophies by Sloan and Brown (1962) and by Krill *et al.* (1973) and is also a well-recognised feature of other dominantly inherited disorders.

As with dominant inheritance, Krill *et al.* (1973) showed that recessive inheritance also has a variable picture, and different affected members of the same family may have different clinical manifestations.

Krill and Deutman (1972) reported 2 families with several members with bull's eye maculae which they believed to be cone degenerations. As well as the typical features several of their patients also had an abnormal EOG and scotopic ERG. Deutman (1974) described a macular disorder of similar appearance inherited as a dominant disease which he called benign concentric annular macular dystrophy. Although this may have a bull's eye appearance, the visual acuity and colour vision are only mildly affected, and the scotopic ERG may be reduced as

well as the photopic ERG and the EOG. As he pointed out, some of these patients had rod involvement as well as cone involvement.

Hittner *et al.* (1975) showed that cone-rod degeneration may initially produce a bull's eye maculopathy and be inherited as a dominant condition. However, their patients progressed and some lost all vision with loss of EOG, photopic and scotopic ERG, and had pigmentary changes in the retinal periphery.

AETIOLOGY

The aetiology of cone degeneration is unknown and may be different in different patients. Dominant and recessive inheritance may be responsible for 2 different types of cone loss even though the clinical manifestations are similar. On the other hand the 2 related patients of this series, who presumably had the same dominantly inherited condition, showed very different clinical pictures, indicating that environmental or constitutional factors must also be relevant to the disease severity. A bull's eye macula with good visual acuity does not necessarily indicate that the cone degeneration is in an early stage, although this may be the case. Also, there may be serious cone malfunction with severe visual and electrophysiological abnormalities with normal fundal appearance (Berson *et al.*, 1968a; Krill *et al.*, 1973; Ohba, 1974).

Diffuse cone loss was probably present in most if not all the present series judging by the abnormal photopic b-waves, but why this should produce a bull's eye appearance is difficult to explain. The photoreceptors and pigment epithelium behave as a functional unit, and diseases of one affect the other as in vitamin A deficiency, retinitis pigmentosa, and myopia. Central pigment epithelial change might be expected to follow cone degeneration as the rod population of the macula is less dense, and conversely the peripheral pigment epithelium would be expected to be relatively normal where the cone population is much less numerous. The central island of more normal pigment epithelium may suggest that there is some overall cone survival, and on account of the high density of cones at the fovea there are sufficient viable receptors to maintain a normal pigment epithelium. This may also explain the relatively good visual acuity, as it is known that loss of half the foveal vision is compatible with normal acuity.

Conclusion

Some patients with acquired cone degeneration may present with clearly identifiable signs, although the visual acuity is good at least in the initial stages. The

presence of marked colour deficiency, bull's eye maculae, and perifoveal annular scotomata should suggest the diagnosis. This may be confirmed by loss of the photopic element of the ERG and a disproportionately affected VER. Other disorders of the receptors and pigment epithelium may produce a similar clinical picture, but electrodiagnostic testing, the clinical progression of the disease, and the age of the patient should help in the differential diagnosis and the identification of pure cone loss.

The patients described in this report have the features of pure cone degeneration. The rod functions appeared to be normal both symptomatically and on electrodiagnostic testing, and there was no pigmentary abnormality in the peripheral fundus as described by Berson *et al.* (1968b) and by Hittner *et al.* (1975).

It would seem, from reviewing these patients and previously described reports, that cone dystrophy may have different aetiologies and that the clinical manifestations may vary within each aetiological group. Further breakdown of the cone dystrophies into different groups may depend on identification of specific biochemical defects.

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