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THE PHOTORECEPTORS IN ATYPICAL ACHROMATOPSIA

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SUMMARY

1. The receptoral mechanisms underlying the vision of two atypical achromats of the complete variety were studied with standard psychophysical procedures.

2. Under scotopic conditions the spectral sensitivity of each achromat was well described by the CIE (Commission Internationale de l'Eclairage) scotopic sensitivity function and the recovery of sensitivity after a retinal bleach showed characteristic duplex behaviour with the time constant of recovery of the slower phase matching that of normal rod vision for both foveal and peripheral stimulation.

3. Their spectral sensitivity was measured under conditions of chromatic adaptation in order to reveal any residual middle or long wavelength cone activity. Only one photopic spectral response was found and this was adequately described by the spectral sensitivity function of Stiles' Π_3 mechanism of normal vision.

4. Increment threshold measurements as a function of background intensity revealed a double-branched function in the fovea. The lower branch was found to have the spectral sensitivity of the rods; the upper branch that of Stiles' Π_3 mechanism. Stiles–Crawford measurements of directional sensitivity confirmed that the branch with the rhodopsin action spectrum had the directional sensitivity of rods and that the branch with the action spectrum of Π_3 had the directional sensitivity of cones.

5. These was no evidence for hue discrimination under photopic conditions. Regions of apparently normal performance on hue discrimination tests on more careful examination could be explained by luminosity judgements mediated by short wavelength-absorbing receptors.

6. We reject the notion of there being rhodopsin-filled cones in the fovea of these subjects. The foveal and peripheral vision of each of these achromats can be adequately described in terms of the participation of only two types of receptor, namely normally functional rods under scotopic conditions and normally functioning short wavelength-absorbing cones under photopic conditions. They are therefore functional blue mono-cone monochromats, an explanation which was originally proposed by Blackwell & Blackwell (1957) over thirty years ago.

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INTRODUCTION

The human visual system processes information along a number of dimensions and our understanding of it has depended on the use of procedures designed to isolate individual elements within this overall process. Traditionally this has been achieved by two different routes: the psychophysical investigation of normal vision and the study of genetic anomalies. For example, Stiles successfully isolated independently adaptable mechanisms (Π mechanisms) in human vision by use of a psychophysical two-colour increment threshold technique (see Stiles, 1959). Genetically, the total and complete achromat has allowed the rod mechanism of normal vision to be studied under conditions where psychophysical isolation procedures are unsatisfactory (Blakemore & Rushton, 1965; Green, 1972; Daw & Enoch, 1973; Nordby, Stabell & Stabell, 1984; Hess & Nordby, 1986*a*, *b*; Hess, Nordby & Pointer, 1987; Nordby & Sharpe, 1988; Sharpe, van Norren & Nordby, 1988; Sharpe & Nordby, 1989; Sharpe, Fach, Nordby & Stockman, 1989). Similarly the study of subjects with dichromatic colour vision has played a key role in understanding the receptoral properties of human colour vision. Neither of these isolation techniques is totally satisfactory by itself for they each have complementary limitations: psychophysical isolation is never complete since it can only be achieved for a limited range of conditions whereas the genetic approach requires an accurate knowledge of the specificity of the pathology.

Another variety of achromatopsia in humans which has great potential for allowing a part of the visual process to be studied in isolation is blue mono-cone monochromacy (Blackwell & Blackwell, 1957). This is very rare, with an incidence thought to be $1:10^6$, and is a type of atypical achromatopsia with an X-linked form of inheritance (Spivey, 1965; Smith, Pokorny, Delleman, Cozijnsen, Houtman & Went, 1983). Although it was initially thought that only normal rods and normal short wavelength-absorbing (S) cones subserved the vision of these subjects and hence the term blue mono-cone monochromacy was adopted (Blackwell & Blackwell, 1961; Alpern, Lee & Spirey, 1965), later studies suggested that they also possessed anomalous foveal cones with an absorbance peak at 505 nm (i.e. rhodopsin cones; Pokorny, Smith & Swartley, 1970; Alpern, Lee, Maaseidvaag & Miller, 1971). The evidence that suggests the presence of rhodopsin-filled cones in the fovea comes from measurements of directional selectivity (Alpern *et al.* 1971) and dark adaptation (Pokorny *et al.* 1970; Alpern *et al.* 1971). Specifically, it suggests firstly the presence of a foveal cone-like directional selectivity associated with a rhodopsin-like spectral sensitivity and, secondly, that the recovery of sensitivity in the fovea following a bleach exhibits a time constant which is more cone-like than rod-like (Alpern *et al.* 1971). It is thought that these receptors are confined to foveal regions although their presence has not been tested for peripherally.

If all the receptors with an absorbance peak at 505 nm are rods, as was originally thought, then these achromats have only one of the three cone types found in normal vision and a careful study of their visual function may reveal a great deal about the contribution made by the short wavelength cones to normal vision. If, on the other hand, some of the receptors with an absorbance peak at 505 nm are normal rods and some are anomalous cones containing the rod photopigment in their outer segment

then this condition is an interesting genetic anomaly but has less application to the study of normal visual function.

There are several reasons for questioning the latter suggestion. Firstly it is based on scant evidence, relying largely on the data for one achromat (Alpern *et al.* 1971). Secondly, Daw & Enoch (1973) were unable to find evidence for rhodopsin cones in a blue-cone monochromat subject: his increment threshold, directional sensitivity and dark-adaptation response at his natural fixation point (2 deg eccentric) could all be explained in terms of normal rod receptors with spectral sensitivity peaking near 500 nm and normal cone receptors with spectral sensitivity peaking near 445 nm. A third reason for questioning the existence of rhodopsin cones in the blue-cone monochromat is that their existence was first postulated in the complete, typical achromat (Alpern, Falls & Lee, 1960; Alpern, 1974), for which there is now evidence to the contrary (Nordby *et al.* 1984; Nordby & Sharpe, 1988; Sharpe *et al.* 1988; Sharpe & Nordby, 1989).

In the present study we examine this question further by undertaking a detailed investigation of two atypical achromats whose clinical characteristics suggest their classification as blue mono-cone monochromats (Blackwell & Blackwell, 1957). We investigate spectral sensitivity under different conditions of chromatic adaptation, dark adaptation, directional sensitivity and hue discrimination to ascertain what type of receptors subserve their vision both peripherally and foveally. In assessing the two key functions of directional sensitivity and dark adaptation on which the previous evidence for the presence of foveal rhodopsin-filled cones depends, we have sought to use stimulus conditions as similar as possible to those used in the original study by Alpern *et al.* (1971). In the foveal region, under conditions which reveal a rod-like spectral sensitivity function we find clear evidence for both a rod-like Stiles–Crawford effect and a rod-like dark-adaptation response. Furthermore under conditions which reveal an S-cone spectral sensitivity function the directional sensitivity is cone-like. Thus our results suggest that the foveal and peripheral vision of these two atypical achromats is subserved by *normal* short wavelength-absorbing cones under photopic conditions and *normal* rods under scotopic conditions and so allows them to be classified as functional blue mono-cone monochromats. The confirmed existence of this rare condition in two subjects now offers a unique means of studying the visual properties of the short wavelength mechanism under genetic isolation and hence of assessing its contribution to normal vision. This is undertaken in the accompanying paper (Hess, Mullen & Zrenner, 1989).

METHODS

Dark adaptation

Pupils were dilated with 1 or 2 drops of tropicamide half an hour prior to testing. The size of the dilated pupil was measured before and after testing with the pupillary measuring attachment of the Goldmann perimeter. A standardized 10 min period of bleaching adaptation was given for a Ganzfeld field which delivered a bleach of 7·3 log scotopic trolands s. Immediately after the period of bleaching adaptation, threshold recovery was measured using the Tübingen perimeter in a dark room. The stimulus was a sharply focused spot of light of dominant wavelength 450 nm. It was either 1·7 deg in diameter and presented at 7 deg from central fixation in the temporal retina or it was 0·25 deg in diameter and imaged on the anatomical fovea. Fixation was maintained by means

of an array of red parafoveal markers whose intensity was reduced as sensitivity recovered. The stimulus was presented abruptly for 500 ms and the subject responded by means of a button when the stimulus was detected. A modified staircase method was used in which the starting location was randomized. The stimulus intensity was changed in 0·1 log unit steps and measurements were continually made for 25–35 min following a bleach.

Spectral sensitivity

Stimulus configuration. A two-beam Maxwellian-view system, with a xenon arc lamp source, was used for determining spectral sensitivity functions in these observers. Monochromatic wavelengths of 8 nm half-bandwidth were generated by using a monochromator (Jobin-Yvon H 20) with an integral stepping motor. Stimulus duration (200 ms) was controlled by an electromagnetic shutter. The light energy leaving the monochromator was variable by means of a circular neutral density wedge with a stepping motor that changed the transmission in steps of 0·05 log units. The transmission of the neutral density wedge and the neutral filters (Schott NG) was calibrated for each wavelength using a calibrated silicon photodiode (United Detector Technology). The diameter of the circular, homogeneous test stimulus was either 8·2 or 0·25 deg, with the focus of the Maxwellian system positioned in the plane of the pupil. It was imaged either 7 deg on the temporal retina or foveally. The adaptation field, 30 deg in diameter and originating from the same xenon arc lamp, was produced using monochromatic filters with a 16 nm bandwidth (Schott AL). The quantal intensity of adapting field was calibrated in units by means of a calibrated photodiode (United Detector Technology) and the values are indicated in the legend for each condition. All functions were controlled by means of a computer (PDP 11/23, Digital Equipment). The subject was lying on an ophthalmological surgical table with his head resting in a head holder. Pupils were dilated by 1 or 2 drops of tropicamide. A cross-hair served to maintain the subject's fixation.

The psychophysical procedure. After 10 min of adaptation to the background field, monochromatic test stimuli were presented every 8 s. Each flash was preceded by an auditory signal. The first flash was below threshold detection. By pressing a button the subject indicated whether he had seen the test stimulus. The wedge transmission was then increased by steps of 0·25 log units until the subject indicated that he had seen the stimulus for the first time. The transmission of the neutral density wedge was then reduced in steps of 0·1 log units using an up-and-down staircase procedure. The procedure was repeated to determine threshold for different wavelengths, increased in 10 nm steps from shorter to longer wavelengths (400–700 nm).

Hue discrimination

Hue discrimination was measured using the Farnsworth–Munsell 100 hue test, administered under two different conditions of illumination. For one condition the test was presented under very bright illumination using two quartz halogen sources (1000 W; Flectalux) which produced a coloured cap luminance of 350 cd m^{-2} and a background luminance of 3000 cd m^{-2}. Natural pupils were used. These conditions produced retinal illuminances above rod saturation (Aguilar & Stiles, 1954; Hess & Nordby, 1986*a*) and so eliminated any rod contributions to the discrimination task. Under the other condition, standard illumination by illuminant 'C' was used, providing a cap luminance of 2·3 cd m^{-2} and a background luminance of 11·7 cd m^{-2}.

Hue discrimination was also measured using a modified Farnsworth–Munsell test consisting of forty coloured caps of equal saturation (chroma) and lightness (value). These caps were from the forty hue test of Lanthony after Farnsworth–Munsell (Luneau Ophthalmologie) and were all presented simultaneously to the subject with no fixed end-points, rather than in the usual arrangement of four separate sections each with fixed end-points. Seven Lanthony neutral (N) caps of different shades of grey (N4 to N7 in steps of N0·5) were included with the forty coloured caps. This test was performed under the conditions of bright illumination described above. Subjects were asked to arrange the caps in order, or groups, according to their similarity of appearance but were otherwise allowed a free hand to choose the manner of arrangement which they preferred (circle, line or otherwise). The scoring of the test was done using the standard Farnsworth–Munsell procedure.

Directional sensitivity

A good way to clarify the presence or absence of 'rhodopsin cones' in the atypical achromat is to investigate the directional sensitivity of their photoreceptors or the Stiles–Crawford effect of the

first kind (SCE_1; Stiles & Crawford, 1933*a*). Since the directional sensitivities of the rods are much smaller than those of the cones (Stiles, 1939; Van Loo & Enoch, 1975; Alpern, Ching & Kitahara, 1983; Nordby & Sharpe, 1988), SCE_1 measurements can be effectively used to determine if the achromats have rhodopsin-filled cones in addition to rhodopsin-filled rods.

Apparatus. The Maxwellian-view apparatus used to measure the SCE_1 has been described previously (Nordby & Sharpe, 1988). It was slightly altered for these experiments. First, instead of a tungsten ribbon filament, a 100 W tungsten–halogen lamp, operated at a constant current of 8 A, was used as a light source. Second, instead of translating the image of the test aperture stop in the subject's entrance pupil by varying the portion of the filament being projected, the image was translated by inserting weak prisms in an appropriate portion of the test beam.

The test field was a monochromatic (λ = 450 nm), 0·47 deg diameter test flash. It was flashed for 200 ms once every 2·5 s; and was presented against a monochromatic (λ = 540 nm), 16 deg diameter background field. The diameter of the image of the test aperture stop in the plane of the entrance pupil was 1·8 mm; that of the background field aperture stop was 1·9 mm.

Procedure. Before beginning each experimental session, the subject had his right pupil dilated with one or two drops of 0·5% tropicamide (Mydriaticum, Roche). Then he dark-adapted for 30 min. First, an increment threshold curve was determined with both test and background aperture stops imaged at the centre of the entrance pupil. The subject's head was held fixed with a bite board and the position of pupil entry was monitored with respect to the reflected corneal images of the aperture stops. Fixation was achieved by placing in the target plane of the large background field four tiny lights in the shape of a cross. They were situated about 1 deg from the centre of the target flash and the observer was instructed to fixate their centre. An increment threshold measurement consisted in setting a neutral density wedge so that the test flash was just visible, the mean of five independent settings being taken. After each measurement the background intensity was raised and the observer light-adapted to a new field for 3 min before beginning the new measurement.

The SCE_1 measurements were made by the same procedure; the only difference being that the image of the test aperture stop was translated along the horizontal meridian of the eye. Threshold determinations were made in a random sequence at several peripheral entry points, ranging from 0 to 3·75 mm on both the temporal and nasal sides of the pupil.

Achromat P.S. did not require his spectacles during the measurements, but achromat S.B. did. For him, therefore, correction was made experimentally for the effect of the lens on the position of the entrance pupil and computationally for the location of the aperture images in the entrance pupil.

Data treatment. The directional sensitivity data were uncorrected for losses in the eye, resulting from reflection at the cornea or from absorption in the lens (see Nordby & Sharpe, 1988). They were standardized to the peak value in the data set and fitted, by the method of least squares, by the parabolic equation (Stiles, 1937):

$$log_{10}\eta = -p(r-r_m)^2. \quad (1)$$

In this equation, η is the directional sensitivity, p is a measure of the directional effect, r is the point of entry (mm) and r_m is the point of entry (mm) for maximal λ.

Clinical details of subjects

Subject P.S., male, 15 years old. His uncle was colour defective, so that an X-recessive inheritance of the colour defect seems probable. The mother reports that the subject suffered from nystagmus during the first year after birth. The nystagmus was considerably reduced after he started reading. He does not complain about major visual problems except reduced visual acuity.

Visual acuity of the right eye was 6/36 corrected with +1·75 sph/−2·25 cyl, at 20 deg, and for the left eye, 6/36 corrected with +1·75 sph/−2·0 cyl, at 145 deg. Intraocular pressure was normal (18 mmHg in both eyes). The anterior and the posterior segments of the eye did not show any pathological signs. Ophthalmoscopy revealed a normal optic disc, normal macular structures and normal peripheral fundus in both eyes. Visual fields (Goldmann) revealed normal sensitivity profiles in both eyes. The initial diagnosis made by his ophthalmologists was achromatopsia. Nyctometry (Rodenstock) performed without glaring revealed normal contrast values but highly decreased contrast sensitivity if a glaring light was present. The colour arrangements test (Panel D-15) showed a slight prevalence of errors along the protan axis. During a period of four years none of the ophthalmological parameters showed any alterations. Electroretinography revealed normal

rod functions and considerably reduced cone function. An initial clinical diagnosis of cone monochromacy was proposed on the basis of measurements of spectral sensitivity (Zrenner, Bender & Lorenz, 1987). In the Nagel anomaloscope equations were made along an axis typical for achromatopsia. The investigation of his mother did not reveal any ophthalmological pathology or functional defects. The second case is remarkably similar to the first one.

Subject S.B., male, 15 years old. There is no family history of any eye pathology. In the first three months of his life the mother reports to have observed horizontal nystagmus which disappeared at age two. He also does not complain of visual problems except low visual acuity. Initially the ophthalmologist's diagnosis, based on ERG, was 'congenital cone dystrophy'. His visual acuity was 6/36 in the right eye (−6·0 sph/−1·0 cyl, at 40 deg) as well as in the left eye (−4·5 sph/−0·75 cyl, at 10 deg). There was a minimal exotropia as well as some remaining binocular stereo vision (Titmus Ring 1 and 2 positive). All other parameters were identical to the previous subject. He also produced an achromatopsia axis on the Nagel anomaloscope. With the Rodenstock Nyctometer this subject was slightly sensitive to glare.

RESULTS

The fixation pattern for the right eye of the two achromats is displayed in Fig. 1 in terms of fixation fundus photographs. A series of fundus photographs were taken such that the fixation target (either the end of a rod or a small bull's eye) was conjugate with the retina. Owing to the off-axis illumination system of all fundus cameras the foveal reflex cannot be seen; however, the centration of the fixation marker relative to the avascular and more deeply pigmented macular region gives a good estimate of fixation. Achromat S.B. exhibited central fixation (Fig. 1*A*) with each eye. Achromat P.S. exhibited a small (2 deg) vertical misalignment in his fixation (Fig. 1*B*) with each eye. Neither subject exhibited observable nystagmus (< 1 deg) when attempting steady fixation.

Scotopic function

As a first step towards understanding which photoreceptors subserve the scotopic function of these atypical achromats we measured their spectral sensitivity under scotopic conditions. The stimulus was a spot 8·2 deg in diameter, imaged 7 deg into the temporal retina of the right eye of each of the achromats. The results are displayed in Fig. 2 in which the reciprocal quantal intensity required for threshold detection is plotted against the wavelength of the stimulus. The results for the two achromats are very similar and well described by the CIE scotopic sensitivity function of normal vision (continuous curve). This suggests that the scotopic mechanism subserving peripheral vision in these achromats has the action spectrum of rhodopsin (Alpern, 1971). Results for foveal vision are given later.

The next question concerns the issue raised in the introduction of whether the rhodopsin is contained in rod or cone photoreceptors in the fovea. The evidence which suggests that it may be contained in cone receptors comes partly from dark-adaptation studies in which it has been found that the form of foveal recovery of sensitivity after a bleach is that expected of cones rather than rods (Alpern *et al.* 1971). We set out to assess this for foveal and peripheral regions of the retina. In our foveal measurements we used stimulus conditions (a spot of 0·25 deg diameter and 450 nm wavelength) which closely resembled those of Alpern *et al.* (1971) and for which a cone-like recovery function had been found.

We first define the normal range for the recovery of sensitivity under our

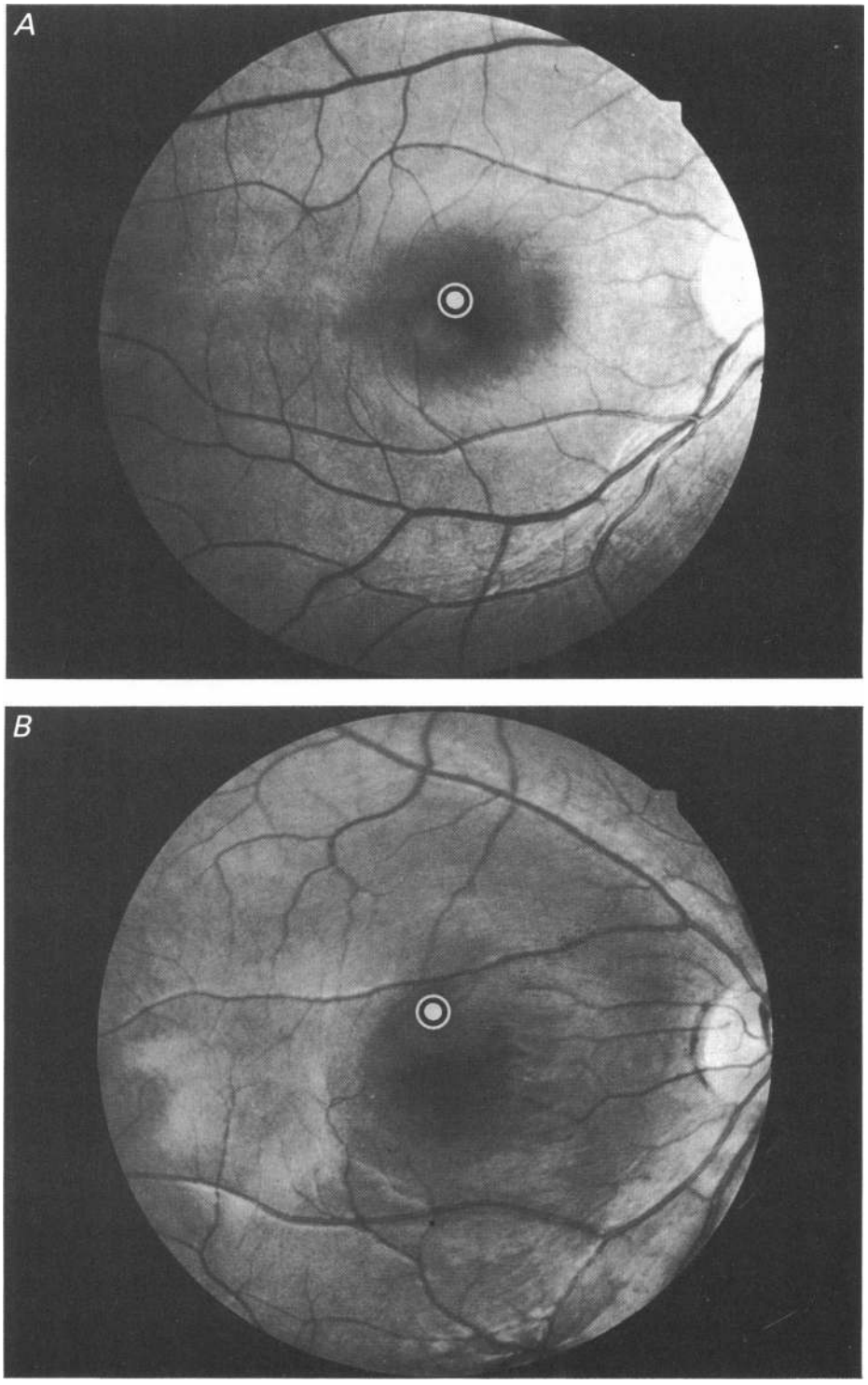

Fig. 1. Fixation photographs for the right eye of the two atypical achromats. Achromat S. B. exhibits central fixation in each eye (right eye shown in *A*). Achromat P.S. has a 2 deg vertical eccentric fixation in superior retina in each eye (right eye shown in *B*).

experimental conditions (see Methods). The results for normal eyes are displayed in Fig. 3. Each panel shows the results of a different subject and results for foveally (*A* and *B*) and peripherally (*C*–*H*) located test stimuli are shown. The relative threshold luminance of the test spot in log units is plotted as a function of the time after a

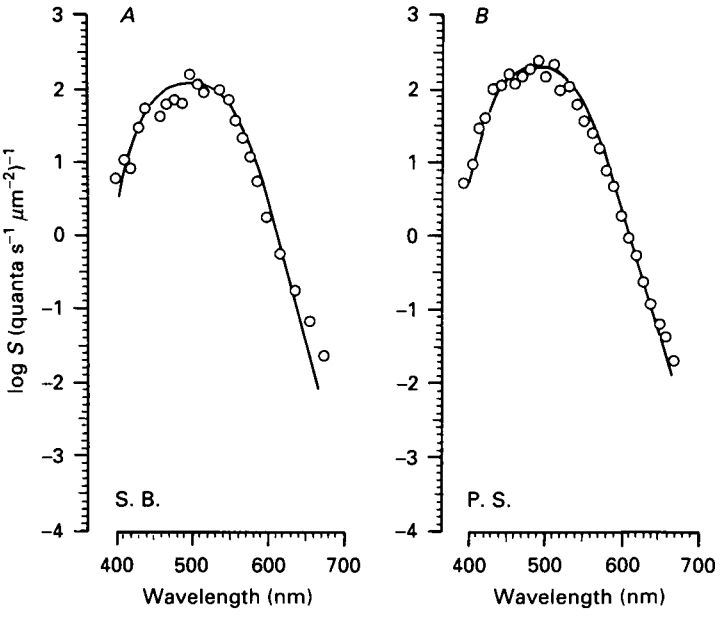

Fig. 2. Spectral sensitivity at absolute threshold for the right eye of each achromat. The reciprocal quantal intensity (quanta s^{-1} μm^{-2}) of the test stimulus at threshold (*S*) is plotted against its wavelength. The stimulus is a spot of 8·2 deg in diameter imaged 7 deg into the temporal field. The continuous curve is the CIE scotopic sensitivity function for normal vision.

bleach. The recovery of sensitivity in the dark after a bleaching stimulus has the biphasic form characteristic of duplex function (Rushton, 1961). The second recovery phase which for normal vision is known to be due to rod photoreceptors was described in terms of the time constant of the best-fitting exponential. The best-fitting exponential is indicated by the dashed line in each of the panels. This is summarized in Table 1 for normal eyes. The average recovery time constant for foveal stimulation was 6·71 min and for peripheral stimulation was 6·38 min ($\pm$0·54). These recovery time constants are in good agreement with previous results in the literature for rhodopsin regeneration. For example, Rushton (1961) found it to be 6 min, Ripps & Weale (1969) found it to range between 4 and 5 min and more recently Pugh (1975) found it to be around 6·4 min for a comparable bleaching light.

The results of the foveal and peripheral dark adaptation measurements on each of the achromats is seen in Figs 4 and 5. The foveal results are for the right eye of each achromat whereas the peripheral results are for each eye of each achromat. Panels *A* and *B* refer to foveal results for a stimulus 0·2 deg in diameter for the right eye, panels *C* and *D* refer to peripheral results for a stimulus 1·7 deg in diameter for the right eye, and *E* and *F* refer to peripheral results on the left eye. Again the dashed curves represent the best-fitting exponentials for the slower recovery curve whose time

constants are given in Table 1. It is clear from an examination of Table 1 that the recovery of sensitivity following a bleach in the eyes of these achromats is very similar to that of normal vision and corresponds to the kinetics of rhodopsin (Rushton, 1961; Ripps & Weale, 1969; Pugh, 1975). Thus, these results are consistent with the scotopic function of these achromats being subserved by normally functioning rod receptors in foveal and peripheral regions of the retina.

TABLE 1. Results for the recovery of sensitivity after a retinal bleach summarizing the data of Figs 3–5. The time constants of the best fitting exponential curves for foveal and peripheral stimulation are given for normals and achromats

Normals				Achromats			
Subject	Eye	Time constant	Mean time constant	Subject	Eye	Time constant	Mean time constant
			Fovea				
S.N.	R	8·11	6·71	P.S.	R	7·94	7·80
R.H.	R	5·32			R	7·75	
				S.B.	R	7·20	7·17
					R	7·14	
			Periphery				
R.H.	R	6·07		S.B.	R	5·23	5·44 (±0·21)*
	L	5·66				5·65	
K.M.	R	7·06	6·38 (±0·54)*		L	5·54	6·64 (±1·10)*
T.M.	R	7·10				7·75	
E.Z.	R	6·01		P.S.	R	9·13	7·29 (±1·80)*
O.M.	R	6·38				5·46	
					L	5·84	6·39 (±0·55)*
						6·94	

*Values (±1 S.D.)

Photopic function

We next considered the photopic function of these achromats and asked whether there is any evidence for the presence of more than one functional cone photoreceptor. A suitable test for the presence of functional middle and long wavelength-absorbing photoreceptors is to measure spectral sensitivity under different conditions of chromatic adaptation (Stiles & Crawford, 1933*b*). Spectral sensitivity results under conditions of blue–green ($\lambda = 489$ nm) chromatic adaptation are displayed for each achromat at a variety of retinal loci (Figs 6*A* and 7*A* and *B*). This wavelength of background field will produce a relative decrease in sensitivity of short wavelength cones and hence reveal any residual middle or long wavelength cone activity. The continuous curve, which provides a good fit to all of the results, is the spectral sensitivity curve of the Π_3 mechanism of Stiles (1953) which is thought to represent the response of short wavelength-absorbing receptors (Pugh & Mollon, 1979). The extent to which these results are well described by this function suggests that middle and long wavelength-absorbing cones are not functioning in the eyes of these two achromats.

Under conditions of yellow chromatic adaptation we could reveal the short wavelength receptoral response in its fullest form because its sensitivity will be

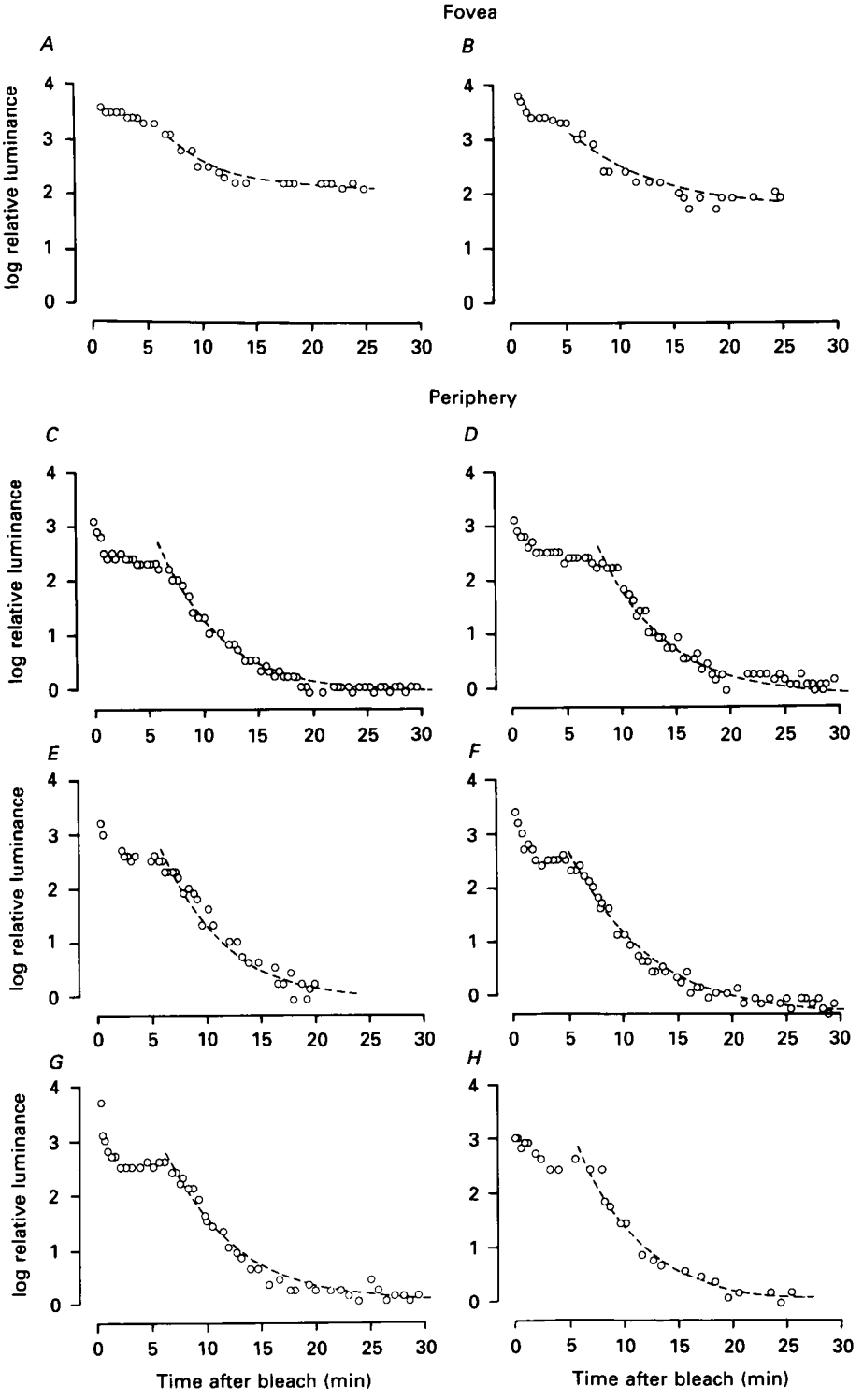

Fig. 3. For legend see facing page.

relatively high, and in the normal eye any middle or long wavelength receptoral responses are desensitized. The spectral sensitivity of the two achromats under these conditions are shown in Figs 6*B* and 7*C*. The shape of the response is the same as that obtained for the short wavelength (489 nm) adapting field and it is again adequately fitted by the Π_3 Stiles mechanism (continuous curve) over 4 log units of its range.

Purple chromatic adaptation will tend to reveal any residual middle wavelength-absorbing cone activity since it reduces the sensitivity of short and long wavelength-absorbing receptors. The spectral sensitivities of the achromats under purple chromatic adaptation are displayed in Fig. 6*C* and 7*D*. The curve has a double peak which can be adequately described by a combination of the Π_3 curve and the CIE scotopic function. Under these conditions the rods are neither saturated nor greatly desensitized by the spectral composition of the background and can contribute to threshold detection at longer wavelengths. While it is possible to account for the departure of the results from the Π_3 curve at wavelengths about 500 nm by assuming that threshold is mediated by a combination of rod and short wavelength-absorbing cone activity, it is not possible to account for the discrepancy by assuming that middle or long wavelength-absorbing cones are participating in detection. This finding confirms previous reports of the mesopic function of these subjects (Blackwell & Blackwell, 1961; Pokorny *et al.* 1970). When taken together these spectral sensitivity responses indicate that the two achromats possess only one class of functional cones whose spectral response matches that of the short wavelength-absorbing receptors of normal vision.

Increment threshold and directional sensitivity measurements

We first determined the foveal increment threshold of the two achromat observers. The target and background conditions were almost identical to those used by Alpern *et al.* (1971): a 0·6 deg blue (450 nm) centrally fixated target was seen in Maxwellian view against a 40 deg green (524 nm) background. The target was flashed for 200 ms once every 2 s. The observer's fixation was aided by fine cross-hairs focused in the plane of the background field. For achromat P.S., who has a 2 deg vertical eccentric fixation in the superior retina, the target was presented 2 deg above the cross-hairs so that it fell on his anatomical fovea.

The results are shown in Figs 8 and 9. For both achromats, the curve is two-branched with the transition occurring near a background intensity of 0·50 $\log_{10}$ scotopic trolands. Spectral sensitivity measurements were made at background intensities above and below the transition to determine the photopigment characteristic of the photoreceptors responsible for the two branches. This was done by finding the increment theshold for different wavelengths of the target, from 390 to 710 nm in 10 nm steps.

Fig. 3. Dark adaptation curves are displayed for normal eyes. Relative luminance (log units) at threshold detection of the test spot is plotted against time (min) after a bleach. The stimulus is a spot of light ($\lambda = 450$ nm) either 0·25 deg in diameter imaged on the anatomical fovea (*A* and *B*) or 1·7 deg in diameter imaged 7 deg into the temporal retina (*C–H*). The pre-adaptation light produced a 7·3 log scotopic trolands bleach. The dashed curves are the best-fitting exponential to the slower recovery phase.

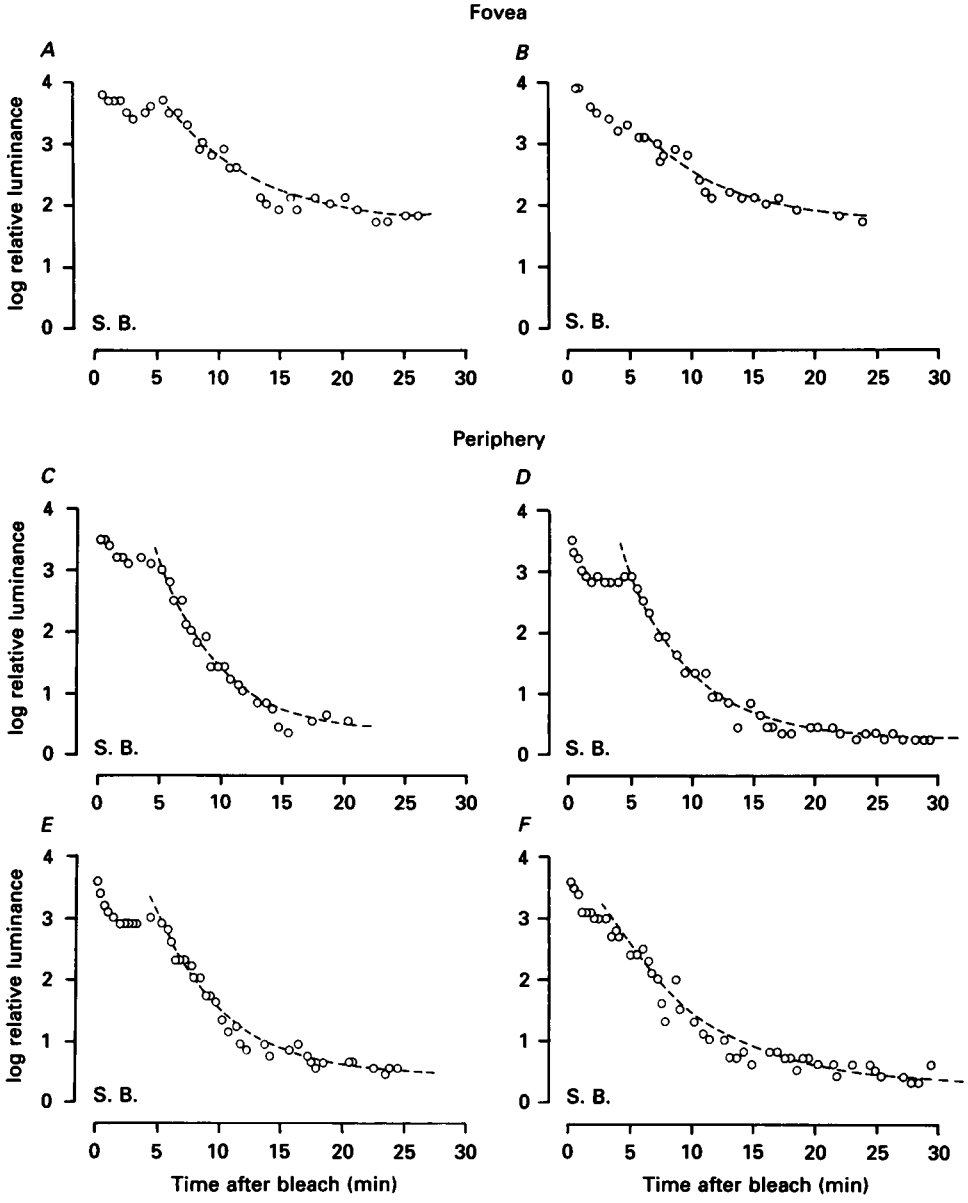

Fig. 4. Dark-adaptation results for achromat S.B. The stimulus is a spot of light (λ = 450 nm) either 0·25 deg in diameter imaged on the anatomical fovea (*A* and *B* show two runs for the right eye) or 1·7 deg in diameter imaged 7 deg into the temporal retina (*C* and *D* show two runs for the right eye and *E* and *F* two runs on the left eye). Relative luminance, (log units) at threshold detection is plotted against time (min) after a bleach. The dashed curve is the best-fitting exponential to the slower recovery phase.

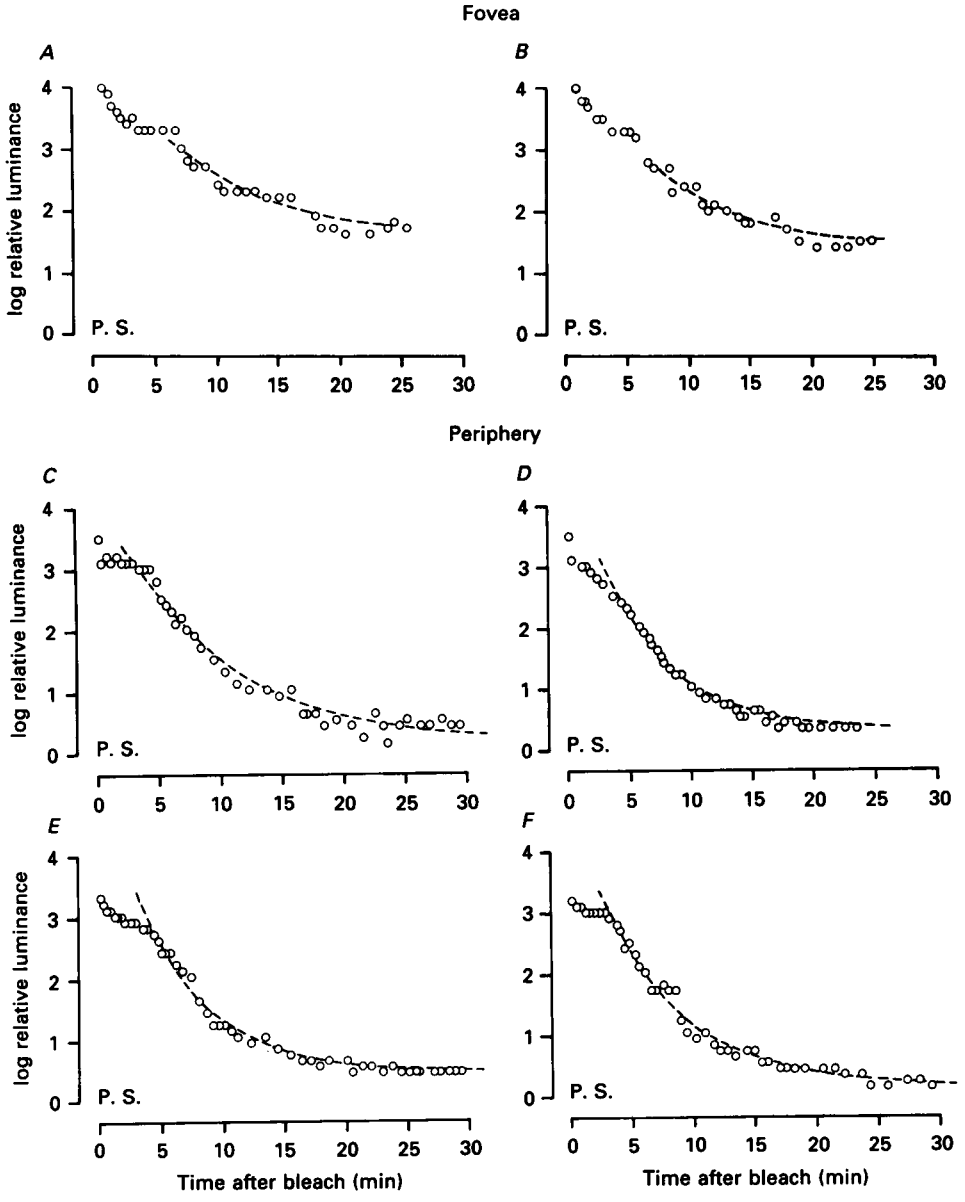

Fig. 5. Dark-adaptation results are displayed for achromat P.S. The stimulus is a spot of light ($\lambda = 450$ nm) either 0·25 deg in diameter imaged on the anatomical fovea (*A* and *B* show two runs for the right eye) or 1·7 deg in diameter imaged 7 deg into the temporal retina (*C* and *D* show two runs for the right eye and *E* and *F* two runs on the left eye). Relative luminance (log units) at threshold detection is plotted against time (min) after a bleach. The dashed curve is the best-fitting exponential to the slower recovery phase.

The measurements establish that the lower branch has the spectral characteristics of the normal rods; whereas the upper branch has the spectral characteristics of the normal blue-cone mechanism (see Figs 8 and 9, insets). For observer S. B. (Fig. 8), at the lowest background tested ($-0{\cdot}16\ \log_{10}$ scotopic trolands), the spectral sen-

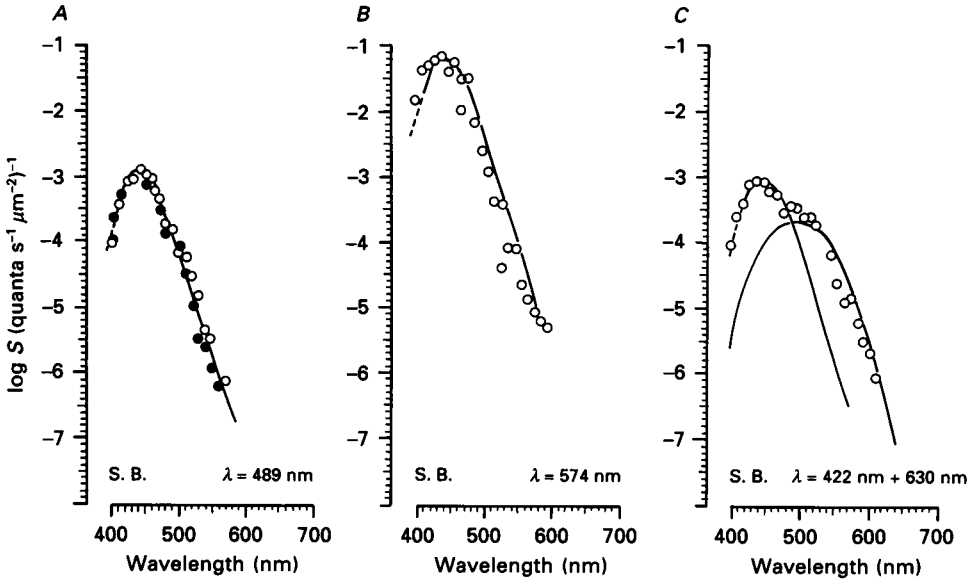

Fig. 6. Spectral sensitivity is displayed under three conditions of chromatic adaptation for achromat S. B. In each panel the reciprocal quantal intensity (quanta $s^{-1}\ \mu m^{-2}$) of the test spot at threshold is plotted against its wavelength. In *A*, results are shown for blue–green (489 nm) chromatic adaptation with a background field intensity of 4·31 log quanta $s^{-1}\ \mu m^{-2}$; in *B* for yellow (574 nm) chromatic adaptation with a background field of 4·35 log quanta $s^{-1}\ \mu m^{-2}$; in *C* for purple chromatic adaptation with a background field of 4·72 log quanta $s^{-1}\ \mu m^{-2}$. The purple filter has two peaks in transmission at 422 and 630 nm. The continuous curve which peaks around 440 nm is the Π_3 mechanism of Stiles whereas the continuous curve peaking at 505 nm is the CIE scotopic spectral sensitivity function. The open symbols are for the right eye and the filled symbols are for the left eye. In all cases the stimulus was a spot 8·2 deg in diameter imaged 7 deg eccentrically on the temporal retina.

sitivities are well fitted by the quantized scotopic luminosity function, shifted only along the axis of the ordinates and corrected for a modest amount of macular absorption. The correction for macular absorption was made according to the mean optical density values of the macular pigment given in Table 2 (2.4.6) of Wyszecki & Stiles (1982, p. 112), assuming a maximum density of 0·5 log units at $\lambda = 458$ nm. (The correction has the effect of shifting the peak of the scotopic luminosity function to 520 nm, which accords with what we found experimentally.)

At the highest background tested ($1{\cdot}84\ \log_{10}$ scotopic trolands), the spectral sensitivities match the relative mean field sensitivities of the π_3 cone mechanism of Stiles (Wyszecki & Stiles, 1982, Table 2 (7.4.3), p. 533). At the two intermediate background intensities ($0{\cdot}12$ and $1{\cdot}0\ \log_{10}$ scotopic trolands), the spectral sensitivities can be fitted by a combination of the Π_3 and the (corrected and quantized) scotopic

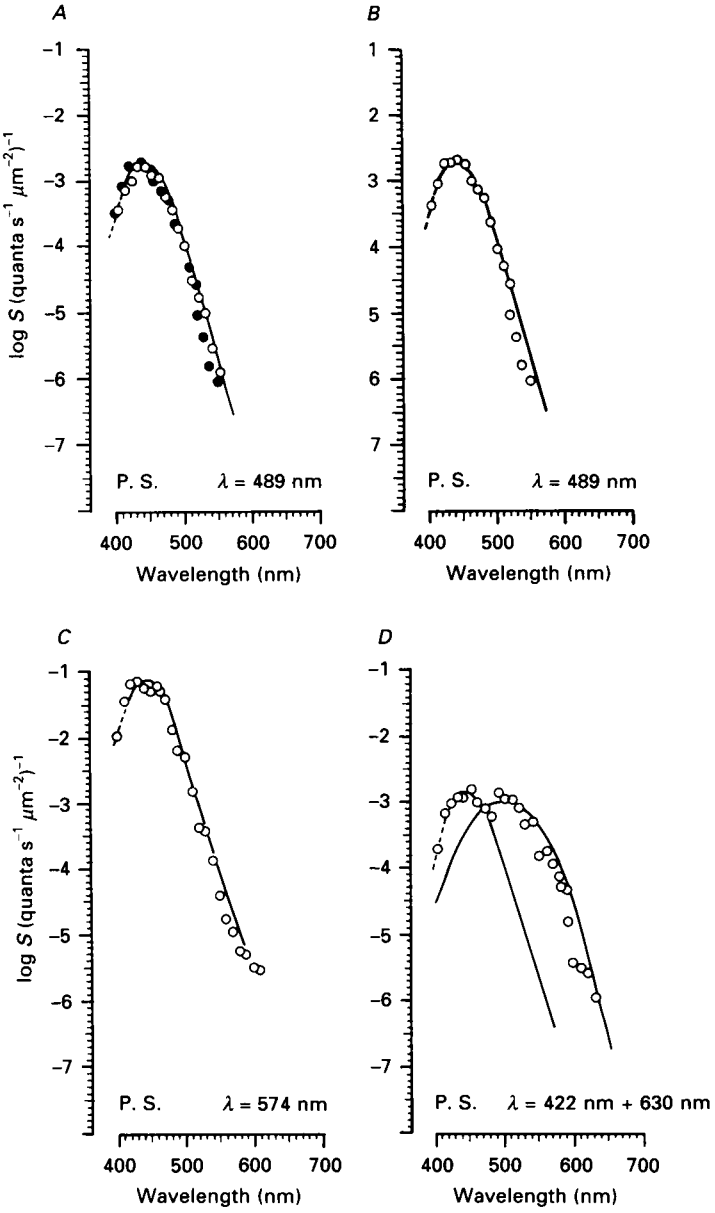

Fig. 7. Spectral sensitivity is displayed under three conditions of chromatic adaptation for achromat P.S. for a spot stimulus 8·2 deg in diameter. In each panel, the reciprocal quantal intensity of the test spot (quanta s^{-1} μm^{-2}) is plotted against its wavelength. In *A*, results are shown for short-wavelength chromatic adaptation for a stimulus imaged on the anatomical fovea (●) and the point of natural fixation (○). In *B* results are shown for short-wavelength chromatic adaptation for a stimulus imaged 7 deg into the temporal retina. In *C* results are shown for middle-wavelength chromatic adaptation for a stimulus imaged 7 deg into the temporal retina and in *D* for combined short- and long-wavelength (purple) chromatic adaptation also for peripheral stimulation with the same background fields given in the legend of Fig. 6. The continuous curve which peaks around 440 nm is the Π_3 mechanism of Stiles whereas the continuous curve which peaks around 505 nm is the CIE scotopic spectral sensitivity function.

luminosity function. This suggests that in the fovea, as in the peripheral retina (see above), as one goes from lower to higher adaptation levels, there is an orderly transition from threshold being mediated by the normal rods to threshold being mediated by the normal blue-cone mechanism.

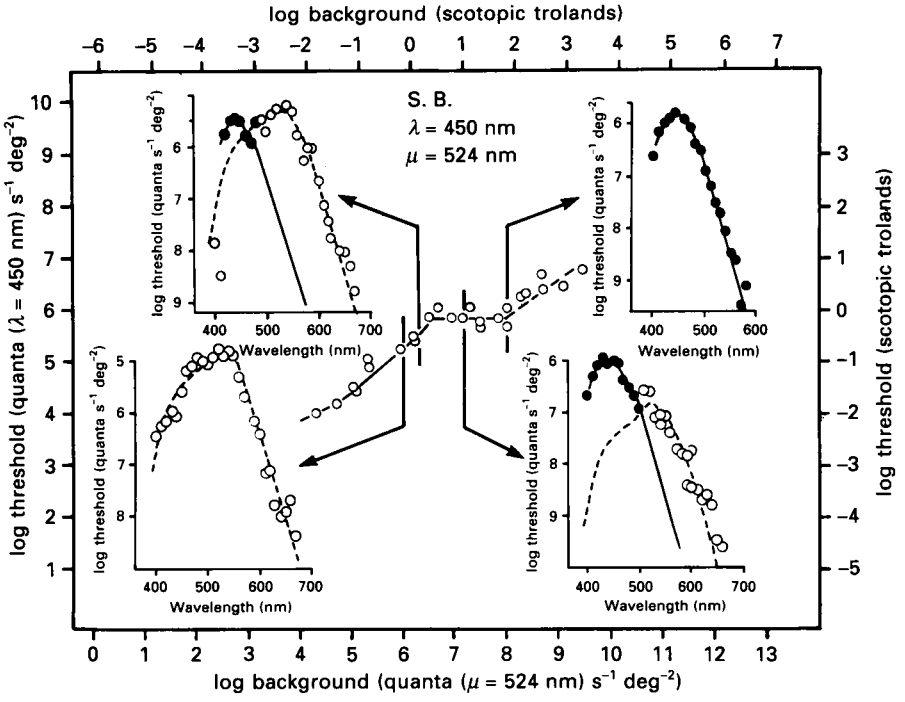

Fig. 8. Foveal increment threshold (middle curve) for a blue ($\lambda = 450$ nm) target presented on a green ($\mu = 524$ nm) background for achromat S. B. The target was 200 ms in duration and subtended a visual angle of 0·6 deg; the background subtended a visual angle of 40 deg. The four inset panels show spectral sensitivity functions measured at background intensities of 6·01, 6·30, 7·17 and 8·01 log scotopic trolands (indicated by the arrows). The continuous line is the Π_3 colour mechanism of Stiles; the dashed line the quantized scotopic luminosity function ($V'\lambda$) corrected for a modest amount of macular pigment absorption.

For achromat P. S. spectral sensitivity was measured at two background intensities (0·24 and 1·44 $\log_{10}$ scotopic trolands); his results are shown in Fig. 9. Results similar to those of S. B. are found indicating that thresholds are mediated by rods before the break and S cones after the break in the incremental threshold function. Furthermore, our measurements accord with foveal increment thresholds made in other blue-cone monochromats by Alpern *et al.* (1971), which indicate that the photoreceptors responsible for the lower branch has the spectral sensitivity of the rods and that the photoreceptor responsible for the upper branch has the spectral sensitivity of the blue cones.

We next measured the directional sensitivity of the mechanisms determining the two branches of the incremental threshold curves. Firstly, however, the foveal increment threshold function was remeasured for both achromats and a normal

trichromat using the Maxwellian-view apparatus which was to be used to measure the directional sensitivities (see Figs 10, 11 and 12; central curves). The target and background conditions were the same as in the earlier measurements, except that the target diameter was 0·5 deg (instead of 0·6 deg), and the background field had a wavelength of 540 nm (instead of 524 nm). In Figs 10 and 11, it can be seen that once again the increment threshold measurements made for central fixation reveal a curve with two branches whereas for the trichromat (Fig. 12) a triple-branched curve is seen.

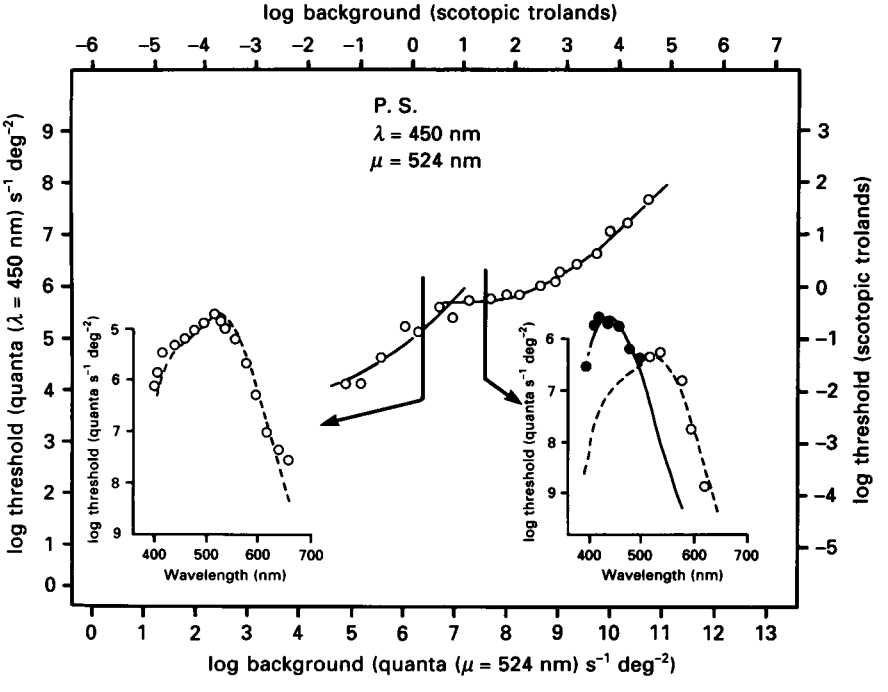

Fig. 9. Anatomical foveal increment threshold for achromat P.S. (middle curve). Details of the stimuli are given in Fig. 8. The inset panels show spectral sensitivity functions measured for the same target and background conditions at background intensities indicated by the arrows. The continuous line fitted to the spectral sensitivity functions is the Π_3 colour mechanism of Stiles; the dashed line is the quantized scotopic luminosity function ($V'\lambda$) corrected for macular pigment absorption.

The key issue here in relation to Alpern's work (see Introduction) is whether rhodopsin is contained in rod or cone photoreceptors in the fovea of these achromats. A comparison of the directional sensitivity results for the lower branch of the incremental threshold curve of the two achromats (Figs 10 and 11) with that for the normal trichromat (Fig. 12) demonstrates that these receptors are rods and not cones. The ordinate in each of these figure insets show the log of the relative intensity (η) required for threshold visibility of a 450 nm target for various positions of pupil entry (r in mm) as shown on the abscissa. The p coefficients (eqn 1) of the best-fitting parabolas drawn through the points are 0·017 for P.S., 0·007 for S.B. and 0·01 for the trichromat. These are also in good agreement with, if not a little flatter than, those

of the parafoveal rods of normal observers (Crawford, 1937; Stiles, 1939; Flamant & Stiles, 1948; Van Loo & Enoch, 1975; Alpern *et al.* 1983) and the rods of the typical complete achromat (Nordby & Sharpe, 1988).

The directional properties of the photoreceptors responsible for the upper branch

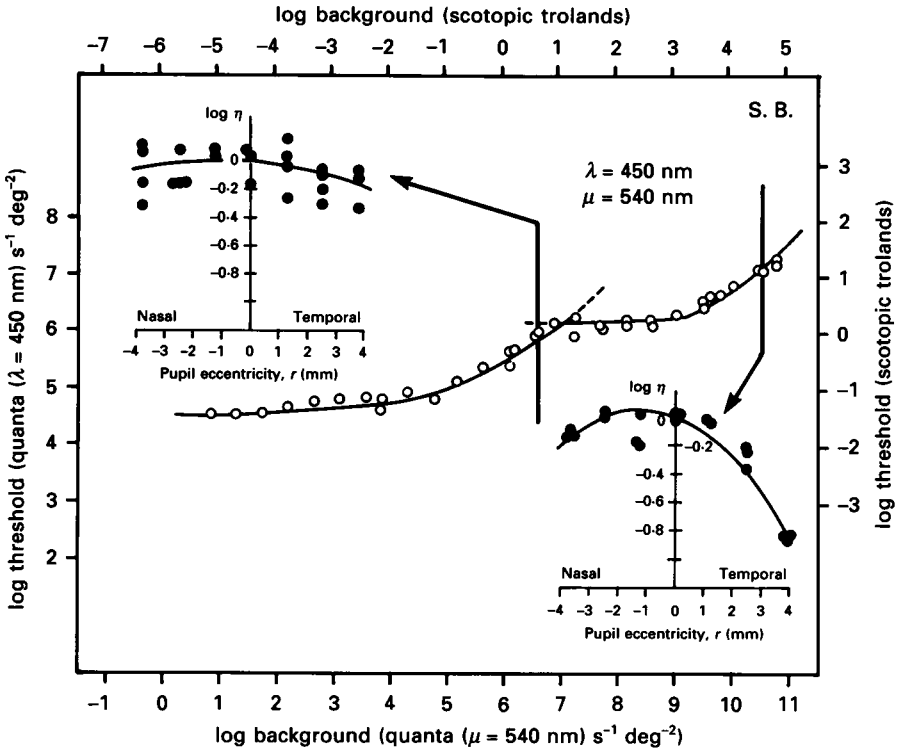

Fig. 10. Increment threshold (middle curve) a blue ($\lambda = 450$ nm) target on a green ($\mu =$ 540 nm) background for achromat S. B. Upper left curve shows the threshold SCE_1 for the same target measured against a 0·68 $\log_{10}$ scotopic trolands background (indicated by arrow). The parabolic curve fitted through the data points has the equation $\log_{10}\eta = -0{\cdot}007\ (r+1{\cdot}02)^2$. The lower right-hand curve shows similar results measured against a 4·65 $\log_{10}$ scotopic trolands background (indicated by arrow). The parabolic curve has the form $\log_{10}\eta = -0{\cdot}032\ (r+1{\cdot}21)^2$.

are much steeper than that just described for the lower branch and resemble those of cones. This is demonstrated in the curve in the lower right-hand insets of Figs 10 and 11 for the two achromats. This curve was measured against a 4·65 $\log_{10}$ scotopic trolands background which is in accordance with the recommendation of Alpern *et al.* (1971) that measurements of the directional sensitivity of the blue cones should be made at backgrounds greater than 4 log scotopic trolands. For both observers, the p coefficients of the best-fitting parabolas, 0·033 for P.S. and 0·032 for S.B., are much larger than those of the parabolas describing the directional sensitivities of the lower scotopic branch.

Figure 12 shows increment threshold and directional sensitivity results for a normal trichromat (L.T.S), measured under the same conditions as for the

achromats. The lowest and highest branches of this triple-branched function correspond to the rods and a short wavelength mechanism respectively; whereas the middle branch corresponds to the Π_4 colour mechanism of Stiles (or the middle wavelength-sensitive cones), which is missing in the achromat. As already described,

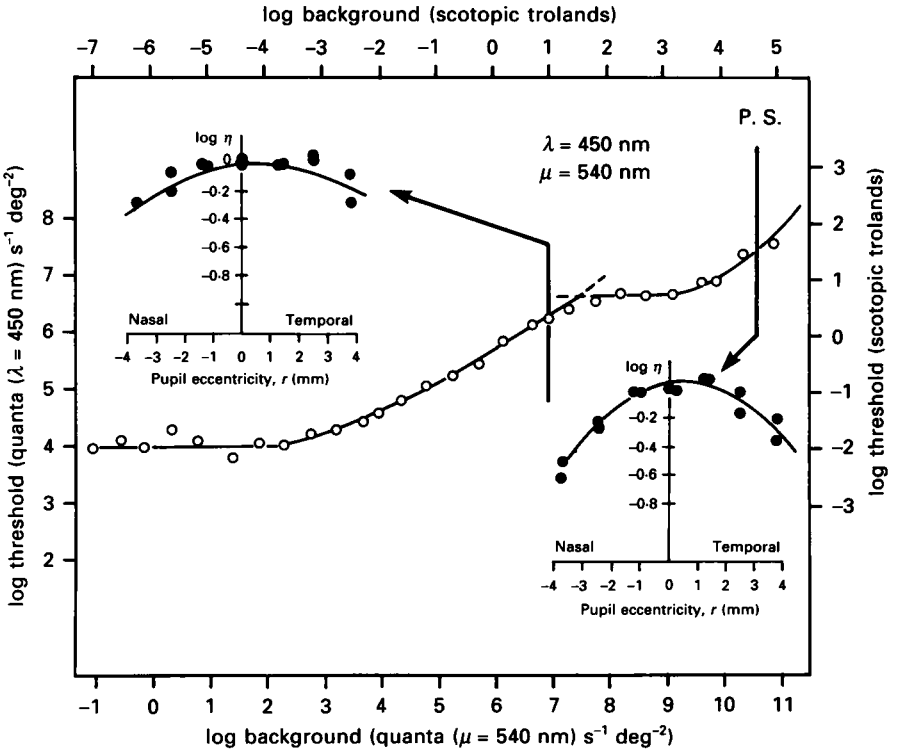

Fig. 11. Increment threshold for achromat P.S. (middle curve). The stimulus conditions are given in Fig. 10. Upper left curve shows the threshold SCE_1 for the same target measured against a 1·0 $\log_{10}$ scotopic trolands background (indicated by arrow). The parabolic curve fitted through the data points has the empirical equation $\log_{10}\eta = -0{\cdot}017\ (r-0{\cdot}55)^2$. The lower right-hand curve shows similar results measured against a 4·65 $\log_{10}$ scotopic trolands background (indicated by arrow), all other conditions remaining the same. The parabolic curve has the equation $\log_{10}\eta = -0{\cdot}033\ (r-0{\cdot}54)^2$.

the directional properties of the photoreceptors determining the lowest branch are typical of those of the rods. The middle branch displays the much more pronounced directional properties of the cones. This is shown in the lower right inset of the figure. The curve was measured against a $-0{\cdot}23$ $\log_{10}$ scotopic trolands background. The p coefficient of the best-fitting parabola has a value of 0·10, which compares favourably to the values (0·073) determined from normal observers at the blue end of the spectrum by Stiles (1937) and Enoch & Stiles (1961).

Both achromat observers display asymmetric SCE_1 functions for the lower and upper branches. For P.S. the centre of symmetry is about 0·5 mm temporal (as measured at the entrance pupil), whereas for S.B. it is about 1–1·2 mm nasal. The greater displacement for S.B. suggests that his photoreceptors are not exactly

aligned with the centre of the exit pupil of the anterior point of the eye, as is the normal tendency (Stiles 1937, 1939; Laties, Liebman & Campbell, 1968; Laties, 1969; Enoch & Hope, 1972). That there is no displacement in the centre of symmetry for either achromat going from a rod-dominated SCE_1 function to a cone-dominated one is consistent with the histological observations that rod and cone orientations are closely related in any retinal region containing both of them (Laties *et al.* 1968; Laties, 1969).

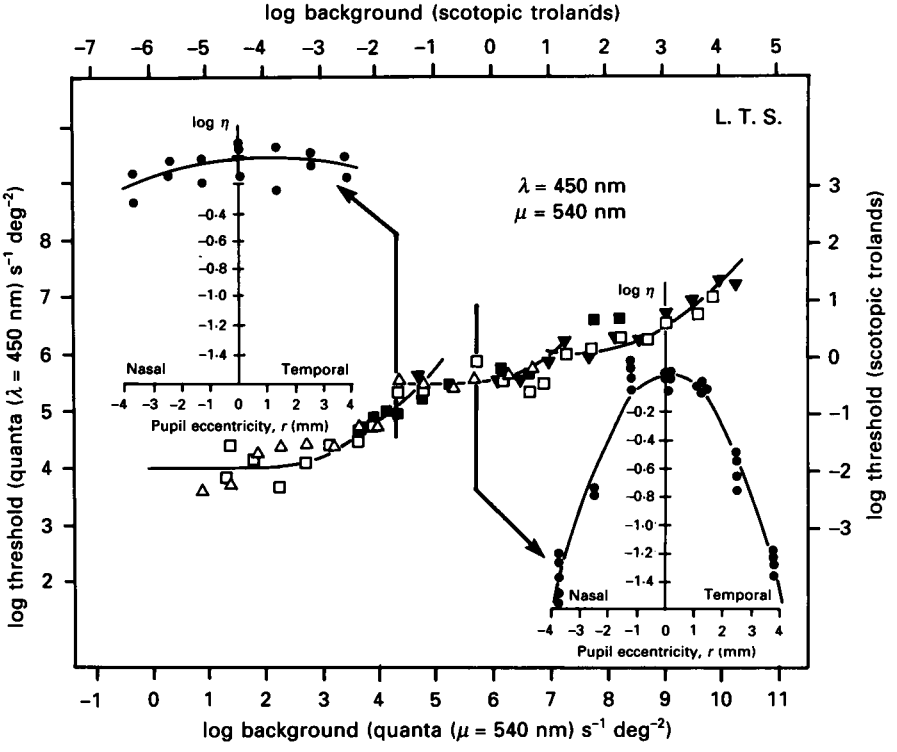

Fig. 12. Increment threshold for normal trichromat L.T.S. (same conditions as in Fig. 10). Different symbols represent separate measurement runs. Upper left curve shows the threshold SCE_1 for the same target measured against a $-1{\cdot}62$ $\log_{10}$ scotopic trolands background (indicated by arrow). The parabolic curve fitted through the data points has the equation $\log_{10}\eta = -0{\cdot}01\ (r-1{\cdot}21)^2$. The lower right-hand curve shows similar results measured against a $-0{\cdot}23$ $\log_{10}$ scotopic trolands background (indicated by arrow). The parabolic curve has the form $\log_{10}\eta = -0{\cdot}10\ (r+0{\cdot}77)^2$.

Colour discrimination

Colour discrimination offers another means by which the mechanisms subserving the photopic vision of these achromats can be explored. It has been claimed that achromats of this general type can exhibit a rudimentary form of dichromatic vision (Blackwell & Blackwell, 1961; Grutzner, 1964; Alpern *et al.* 1971; Daw & Enoch, 1973). The crucial question that must be addressed is whether colour discrimination is possible for these achromats at illuminance levels where rod photoreceptors are known to be saturated (Aguilar & Stiles, 1954; Hess & Nordby, 1986*a*; Hess, Nordby

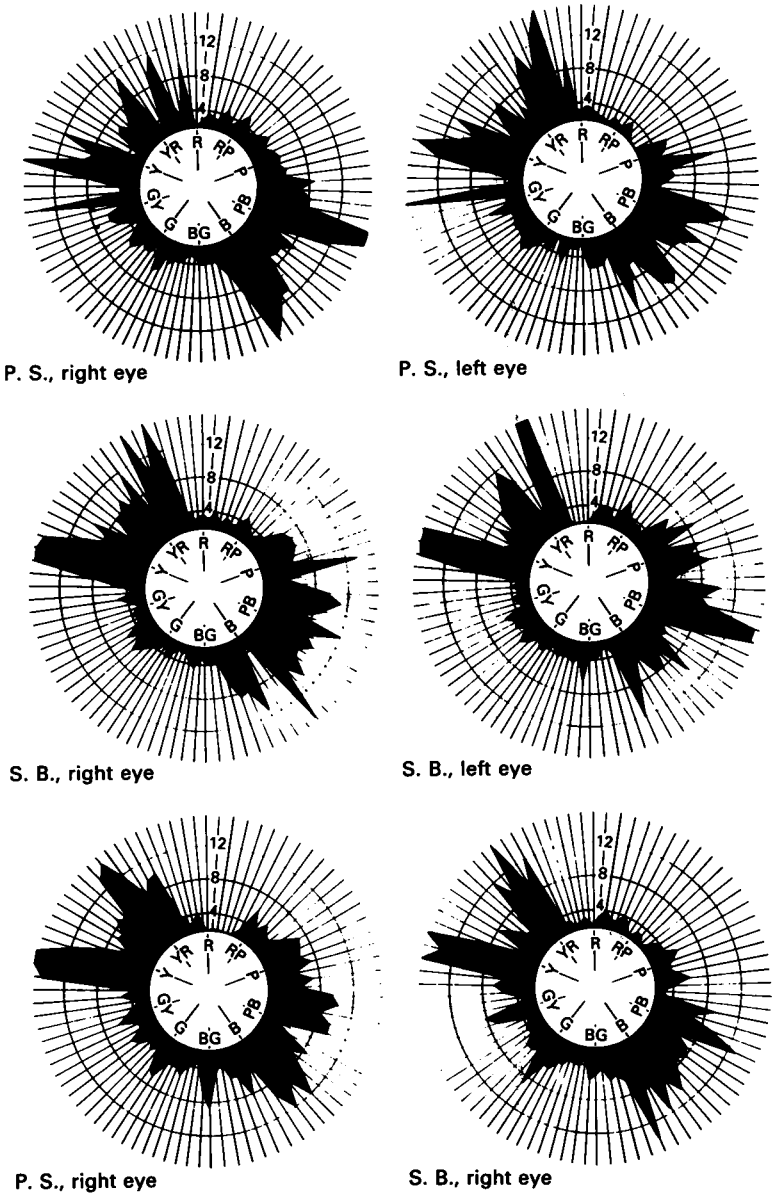

Fig. 13. Error plots for the scores of the Farnsworth–Munsell 100 hue test. Each figure shows the average of two presentations of the test. In the upper and middle panels error plots are shown for the right and left eye of each achromat when the illumination was provided by illuminant C. In the lower panels, the illumination was provided by two quartz halogen spot lights producing an illumination substantially above rod saturation (see Methods). Note that poor discrimination occurs along the B–YR axis and best discrimination (within normal limits) along the G–RP axis. This pattern is the same for each eye of each achromat and it is not substantially altered by the high illumination condition. B, blue; Y, yellow; R, red; G, green; P, purple.

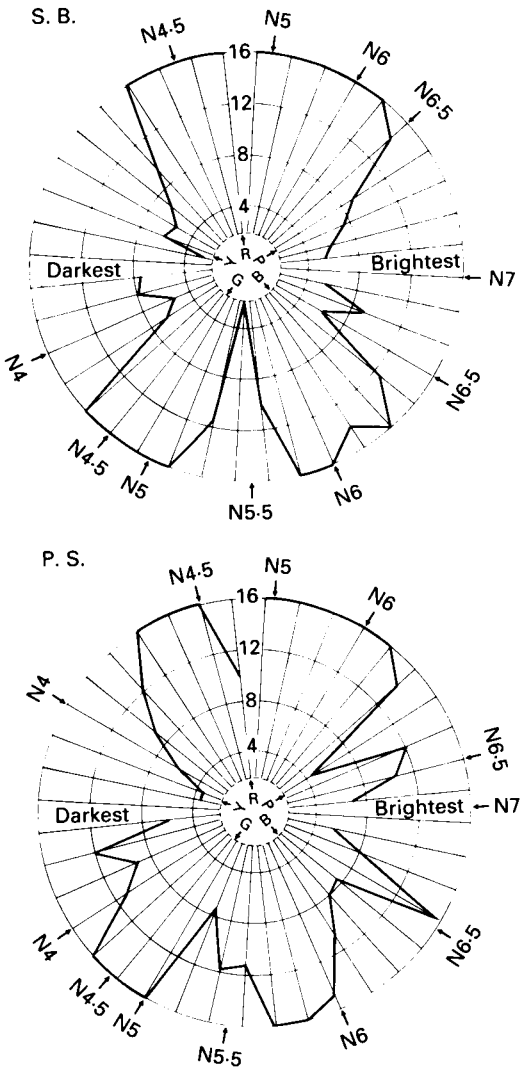

Fig. 14. The results of a modified Farnsworth–Munsell hue discrimination task in which forty hues are presented simultaneously to the subject. Seven neutral grey caps were also included in the task (N7 (light) to N4 (dark) in steps of N0·5). See Methods for details. The results are the average of two runs on the right eye of each achromat. Scoring was done in the usual way and as for Fig. 13. The arrows indicate the position of the neutral caps in the colour sequence (i.e. the positions of the two coloured caps occurring next to each neutral cap were averaged for each side of the colour circle). Note that errors are very great especially around the red and green regions where they were least in Fig. 13. See text for explanation.

& Pointer, 1987). If colour discrimination is possible within this range then the present evidence which argues for mono-cone function for these patients must be rejected.

Most of the available information on colour discrimination in achromatopsia of this form has involved the use of the Farnsworth–Munsell 100 hue test (Farnsworth, 1943) and for this reason we have used the same approach. Figure 13 summarizes the results for colour discrimination using this test. As described in the Methods each achromat was tested under two conditions of illumination: standard illuminant C (upper and middle panels) and very much brighter illumination which was above rod saturation (lower panels). The results of colour normal observers lie around the inner circles, indicating few errors in the sequencing of the coloured caps of the test. The results for the two achromats are similar and are consistent with previously published findings for this test (François, Verriest, Matton-von Leureen, De Rouck & Manevien, 1966; Alpern *et al.* 1971) namely that many errors are made along a blue to yellow–red axis and near normal levels of discrimination are found along the green to red–purple axis. Interestingly, this pattern of results is not substantially altered by conducting the test under illumination conditions well above rod saturation (lower panels), which indicates that it is not due to the participation of rod photoreceptors.

Do the regions of good discrimination indicate that more than one type of cone photoreceptor subserves the vision of these achromats? Before attempting to answer this it is instructive to realize that this Farnsworth–Munsell colour discrimination test is prepared in four separate boxes, in each of which the caps are arranged in colour sequence between fixed local end-points. This divison of the complete colour range for test convenience influences the type of results obtained. For example, the colour range covered by one box of coloured caps covers the region where sensitivity is governed by the short wavelength side of the achromats' spectral sensitivity curve and so is rapidly changing. Another colour range is governed by wavelengths closer to the peak region of the spectral function where sensitivity is flatter, a third range covers a region where sensitivity is rapidly falling at longer wavelengths and a fourth covers the long wavelength region to which the achromats are very insensitive. Thus, the colour regions where discrimination is best on the 100 hue test (see Fig. 13) coincides with the regions where spectral sensitivity is varying most greatly and so it is likely that our subjects can perform well within these ranges solely by making local brightness judgements within *each* box of caps.

We devised a modified hue discrimination task in order to test for the subjects' use of brightness cues. A similar test was used but with only forty colour caps and with the addition of seven neutral grey caps of different luminosities (see Methods). This was administered such that *all* the caps were presented at the same time. The achromats were requested to place all forty-seven caps in sequence of appearance and to identify any caps that did not fit into the sequence. If the 100 hue discrimination was based solely on brightness changes then the colour region where discrimination was previously good will be disrupted because caps of different colours but similar brightnesses are now present within the same test. Furthermore, the neutral greys will not only be accepted as representative 'colours', but will also be sequenced in order of their luminosity in the eventual 'colour' sequence.

The results of such a test are displayed in Fig. 14. These predictions are supported. Discrimination is now very poor for all hues but especially around the red and green colour regions where it was best in the 100 hue test. This is because caps from opposite sides of the colour circle are now freely mixed side by side in the cap sequence producing extremely high error scores. All the neutral caps were readily incorporated into the test by the subjects. Their positions in the cap sequence are indicated by the arrows on the figure and the results show that they are placed in order of their brightness (luminosity). Furthermore, it is interesting that each subject confidently volunteered colour names for various chips including the neutral ones. Both subjects preferred to order the caps in a line sequence, rejecting a circular arrangement, and referred to the two ends as 'hell' (light) and 'dunkel' (dark) and these are marked on the figure. The results confirm that there is no evidence for any hue discrimination by the subjects and that eventual sequence of caps was arranged in order of brightness, as would be expected if only one type of photoreceptor subserves vision under photopic conditions.

DISCUSSION

In this study we have investigated the foveal and peripheral vision of two atypical achromats and demonstrated that it is subserved by normally functioning rods under mesopic and scotopic conditions and by normally functioning short wavelength cones under mesopic and photopic conditions. This supports the original proposal that some of these atypical achromats (Blackwell & Blackwell, 1957) should be classified as blue mono-cone monochromats and as a consequence is in agreement with previously published material on atypical achromats (Blackwell & Blackwell, 1961; Alpern *et al.* 1965; Pokorny *et al.* 1970; Smith *et al.* 1983). Our results do not rule out the possibility that some rudimentary dichromatic vision might be able to be obtained under mesopic conditions owing to the participation of rod receptors (A. Reitner, L. T. Sharpe & E. Zrenner, unpublished observations) and would be consistent with a reinterpretation of the mesopic colour matching results of Alpern *et al.* (1971). However, they show that under photopic conditions, regardless of the fact that colour names are used, the vision of these subjects is achromatic.

Subjects such as this provide a unique opportunity to explore the contribution of the short wavelength-absorbing cones to vision under conditions of genetic isolation, which is undertaken in the subsequent paper. The fact that it has taken more than thirty years for this to be resolved after the original classification by Blackwell & Blackwell (1957) is due to at least two different factors. Firstly it is now clear that not all clinically diagnosed cases of atypical achromatopsia with X-linked inheritance are blue mono-cone monochromats. Some have long wavelength-absorbing cones which can be revealed by measurements of spectral sensitivity and colour matching. They have been referred to as X-linked incomplete achromats (Smith *et al.* 1983). Our results clearly demonstrate that the two subjects studied here are of the complete form and that this does not depend on the region of retina investigated (Blackwell & Blackwell, 1961; Alpern *et al.* 1971).

The second factor was the proposal made by Pokorny *et al.* (1970) and Alpern *et al.* (1971) that the 505 nm-absorbing photoreceptors in the fovea of the eyes of

atypical achromats were cones. Pokorny *et al.* (1970) concluded that there are two 505 nm receptors; 505 nm cones responding at low light levels and 505 nm rods responding at high light levels. Two lines of reasoning led them to conclude that 505 nm cones mediated absolute threshold. Firstly, the threshold at 505 nm did not change with dark adaptation for a 10 min test light. Secondly, the achromat has foveal function for bright test objects as determined by using a visuoscope. Each of these points is open to reinterpretation. Firstly, a very small test object contains energy at a range of spatial frequencies and can in principle be detected by a post-receptoral neurone with large summation areas, whose Weber responses are known to extend to very low luminances (Van Nes & Bouman, 1967). Secondly, the fact that foveal fixation is present does not in itself argue against rods determining threshold. The rod-free area in the primate extends up to 30 min of arc away from the foveal pit. Fixation eye movements of the order of 30 min of arc would enable large centrally located receptive fields with rod contributions to detect the target. In fact under mesopic conditions it is the centre of the visual field that exhibits best contrast sensitivity for rod vision (Hess *et al.* 1987).

Alpern *et al.* (1971) concluded that the 505 nm foveal photoreceptors are cones on the basis of directional sensitivity and dark adaptation. At the time of these measurements it was generally believed that only cones exhibited the property of directional sensitivity and it was only later that Van Loo & Enoch (1972) showed that rods exhibited a limited form of directional sensitivity (see also Nordby & Sharpe, 1988). A subsequent study by Daw & Enoch (1973) on blue mono-cone monochromats showed that the directional sensitivity of their 505 nm absorbing receptors was that expected of normal rods. Furthermore, there is a problem associated with the directional sensitivity measurements made by Alpern *et al.* (1971). Alpern *et al.* (1971) do not explain how well they control for the steadiness of fixation; they only say that fixation was 'central'. All their subjects had a 'fine pendular nystagmus in the primary position'; however, neither of our subjects do. Thus, if fixation had been unsteady, the slopes of the directional sensitivity function measured for their blue-cone monochromat (their Fig. 7) may have been exaggerated due to the test beam being vignetted by the pupil. It is more difficult to account for the very rapid recovery of sensitivity (time constant = 2 min) after bleaching reported by Alpern *et al.* (1971). However, this has not been replicated in other similar atypical achromats (François *et al.* 1966; Daw & Enoch, 1973) nor in the present study.

In the present study we have measured directional sensitivity and dark adaptation using very similar conditions to those of Alpern *et al.* (1971) and our results refute their claim by showing that the rhodopsin-filled receptors in the foveal region of the eyes of these achromats are the scotopic photoreceptors of normal vision, namely rods. However, we are in partial agreement with Alpern *et al.* (1971) in that we find that the foveal photoreceptors functioning under photopic conditions are the short wavelength cones of normal vision. These two conclusions also apply to the peripheral regions of the retina. Thus we conclude that atypical achromats of the type studied here possess two functioning photoreceptors, namely normal rods and normal short wavelength cones.

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