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SPATIOTEMPORAL CONTRAST SENSITIVITY AND COLOUR VISION IN MULTIPLE SCLEROSIS

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SUMMARY

Measures of contrast sensitivity and colour vision were taken from a group of 18 multiple sclerosis patients. Contrast sensitivity losses, measured at 5 spatial frequencies and 4 temporal frequencies, were found to be significant in 11 patients. Red/green (Rayleigh equation) and green/blue (Engelking-Trendelenburg equation) Pickford-Nicolson anomaloscope settings were abnormal in 15 patients. Correlating each of the 20 spatiotemporal losses with the colour losses revealed that in 19 conditions the red/green loss was greater than the green/blue loss. None of the green/blue losses correlated significantly with spatiotemporal losses while between 2 and 8 cycles/deg 11/12 spatiotemporal conditions showed significant correlations with red/green colour loss. These results support a locus of damage before the cortex at a stage in the visual pathway where red/green chromatic information may be encoded in pathways which also code luminance information.

INTRODUCTION

The visual pathway is particularly susceptible to damage in multiple sclerosis (MS). Magnetic resonance imaging (MRI) has revealed damage to the optic tract in some patients (Rosenblatt *et al.*, 1987) and damage to the optic radiations in about two-thirds of patients presenting with a common precursor of MS, optic neuritis (W. I. McDonald, personal communication). Clearly, lesions to the optic nerve, tract and radiations are frequent in this disease. It is precisely these precortical pathways that have been the focus of recent advances in our understanding of the neurophysiology of vision. The convergence of many receptor cells onto relatively few ganglion cells demands an efficient code of information processing along the visual pathway to the visual cortex. Accumulating evidence (Wiesel and Hubel, 1966; De Valois *et al.*, 1977; Ingling and Martinez 1983; Ingling and Martinez-Uriegas, 1985; Derrington *et al.*, 1984) suggests that, within this information processing 'bottle-neck', many parvocellular cells in the lateral geniculate nucleus (LGN) may be transmitting information both about the colour and the luminance of a stimulus: they are performing a 'double-duty'.

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This general view is far from proven. While all experimenters appear to agree that the parvocellular cells, with their overt chromatic opponency, are vital for colour processing, their role in mediating achromatic contrast sensitivity is less well established. The magnocellular pathway, with substantially higher contrast sensitivity, appears to be the better candidate. However, the receptive fields of the cells of this pathway are large and they represent perhaps only 10% of the cells covering the fovea. High contrast sensitivity therefore seems to be combined with poor spatial resolution. Shapley and Perry (1986) claimed that the contrast sensitivity function may reflect the activity of the magnocellular pathway at all but the higher spatial frequencies, but Derrington and Lennie (1984) pointed out that probability summation between as few as 10 parvocellular cells would be needed to regard the contrast sensitivity function as a reflection of the parvocellular pathway. Certainly selective destruction of the parvocellular pathway by acrylamide (Merrigan and Eskin, 1986) does reduce contrast sensitivity by almost a factor of ten.

This debate will doubtless develop in the future. Its relevance for clinical investigations of visual perception in MS is unquestionable; already it has required us to treat studies which have regarded the physiological damage in this disorder in terms of selective loss to X or Y pathways with some caution. Considering these advances, psychophysical tests designed to identify more precisely the site of damage in the visual pathways in MS are of the utmost importance.

Traditionally, psychophysical investigations of the visual losses seen in MS have concentrated on contrast sensitivity or colour vision. The contrast sensitivity deficit for stationary gratings appears to take one of four forms: the contrast sensitivity function may show an overall depression; or the loss may be restricted to gratings of low, medium or high spatial frequencies only (Regan *et al.*, 1977; Frisén and Sjöstrand, 1978; Bodis-Wollner *et al.*, 1979; Zimmern *et al.*, 1979; Hess and Plant, 1986). When gratings are temporally modulated (either drifted at constant velocity or phase alternated) a different picture emerges. Some authors (Brussell *et al.*, 1984) have claimed that the deficit observed for stationary gratings persists unchanged into the temporal domain; others (Plant and Hess, 1985) have argued that the loss of sensitivity decreases at high rates of movement but for gratings of low spatial frequency only; still others (Medjbeur and Tulunay-Keesey, 1985) have found that temporal modulation can increase or decrease the deficit for stationary gratings or interact with spatial frequency and reverse the pattern of results found with stationary gratings. These authors have often interpreted their results within a psychophysical model that proposes channels tuned to some range of spatial and temporal frequencies (Watson and Robson, 1981; Thompson, 1984; Hess and Plant, 1985). However, this approach does not enable the identification of the site of any lesion because spatial and temporal frequency tuning is present at the level of the ganglion cells (Enroth-Cugell and Robson, 1966) as well as in the visual cortex (De Valois *et al.*, 1982).

Ostensibly, colour vision testing offers a more secure method of identifying the site of the lesion in MS. Work by a number of researchers (*see* Pokorny *et al.*,

1979, for a review) permits the identification of the site of physiological damage associated with discrete acquired colour vision deficits, at least distinguishing between receptoral, postreceptoral and cortical locations. Kollner's Rule, for example, states that blue defects are characteristic of retinal disorders and red-green defects of optic nerve disorders. However, the nature of the colour vision deficit in MS has proved elusive. Most workers would agree that, when examined with conventional tests of colour vision, the defect resembles that found in acquired, rather than congenital defects; but the errors may be difficult to specify (Griffen and Wray, 1978), or be confined to a red/green (e.g., Cox, 1961) or 'blue/yellow' (e.g., Ohta, 1970) dimension. In general terms, these correspond to the type II and type III acquired colour vision deficits classified by Verriest (1963). In type II loss discrimination along a red-green axis deteriorates progressively with a concomitant milder blue-yellow loss. The more common type III loss is characterized by a mild or moderate loss of discrimination on what is often called the blue-yellow axis. However, it should be noted that a type III tritan-like deficit actually results in blue/green and violet/yellow confusions and not blue/yellow confusions (*see* Wright, 1979).

Using more sophisticated psychophysical procedures, some experimenters have reported that patients with MS exhibit a larger loss of luminance than chromatic function (Zisman *et al.*, 1978; Alvares *et al.*, 1982). However, others (Fallowfield and Krauskopf, 1984; Mullen and Plant, 1986) have reported that the transmission of colour information is more severely impaired. Still others have reported the losses to be nonselective (Foster *et al.*, 1985; Sellers *et al.*, 1986). These results may be in conflict partly because of the not inconsiderable problem of designing experiments that test independently luminance and chromatic functions, and partly because their model of postreceptoral colour processing requires the separation of chromatic and luminance information within the optic nerve.

If some parvocellular cells are multiplexing both luminance and chromatic information, as discussed above, then these dimensions, far from being transmitted along independent pathways, are encoded by a single pathway that performs 'doubly-duty'. Furthermore, certain acquired defects of colour vision that arise from damage to the optic nerve or tract would go hand-in-hand with contrast sensitivity deficits. Specifically, physiological evidence (Derrington and Lennie, 1984; Derrington *et al.*, 1984) shows that the cells in the parvocellular layers of the lateral geniculate nucleus receiving input from long and middle-wave cones (L-M cells) respond well to colour modulation at low spatial frequencies and luminance modulation at high spatial frequencies. One prediction from this is that, as red/green discrimination deteriorates, so too should contrast sensitivity. Note that 'red/green discrimination' is used here to mean a discrimination depending only on activity in L-M cells, such as a discrimination between a pair of protanopic or deuteranopic metamers. The same physiological work has shown that other parvocellular units (those that receive opposed inputs from short-wave cones and some combination of long and middle-wave cones, i.e., S-(L and M)

cells) are relatively unimportant for spatial vision. We can therefore predict that a deficit on a similar colour discrimination task depending only on activity in S-(L and M) cells (e.g., a discrimination between two tritanopic metamers) should not correlate with a contrast sensitivity loss.

We have measured contrast sensitivity losses and colour discrimination losses in MS patients to ascertain whether the relationships outlined above occur. If such a relationship were found, it would suggest that, at least in the peripheral visual system where damage is most often reported in MS, the psychophysicists' colour and luminance 'channels' do not have separate neurophysiological underpinnings. Such a result would be of obvious importance in any attempt to build a model of optic nerve damage in this disease.

METHODS

Subjects

The clinical subjects were 18 patients with MS, 4 males and 14 females. The patients were 'clinically definite' cases according to the criteria of Rose *et al.* (1976). None of the patients was in an acute phase of their disease. The age range of the subjects was 33 to 63 yrs with a mean age of 46.1 yrs ($\pm$8.9 SD). Informed consent was obtained from all patients. Subjects wore their best optical correction for all experiments.

Control subjects were used in the assessment of colour vision. Two separate control groups were used, drawn from a population of Open University students attending Summer School at the University of York. The control group for the Rayleigh equation (*see* below) consisted of 20 subjects, 9 males and 11 females. The age range of these subjects was 35 to 67 yrs with a mean of 45.8 ($\pm$7.5 SD). The control group for the Engelking-Trendelenburg equation also consisted of 9 males and 11 females. The age range of this group was 38 to 59 yrs with a mean of 46.5 ($\pm$6.9 SD). In order to facilitate comparison with the MS patients, (1) the control subjects performed the anomaloscope test monocularly, but only one eye was tested (the left eye in all except 1 case); (2) subjects were selected to be within the appropriate age range because of the known effects of age on colour vision (e.g., Verriest, 1963). Before testing, subjects were screened for congenital colour deficiency with the Ishihara test for colour blindness and the Farnsworth F2 tritan plate. Two potential subjects, both male, failed this screening test and were not examined on the anomaloscope. It was necessary to use two separate control groups because demands on the students' time meant they could only participate in one experiment.

Contrast sensitivity measurements

Apparatus and stimuli

Computer-generated vertical sinewave gratings were displayed on the screen of a Joyce Electronics display with P4 phosphor. The frame rate used was 100 Hz. The subject viewed a circular, 1.85° diameter patch of grating. Screen luminance, measured with a Minolta Chromameter CS-100, was 100 cd/m^2. Contrasts in the range 0–77% were used.

Procedure

Subjects sat 298 cm from the screen. Precise viewing distance was controlled with a head rest. Subjects were instructed to maintain fixation on a small high contrast dot in the centre of the screen, and natural pupils were used. Viewing was monocular and each eye was tested in turn. In most of our patients we were able to obtain more than one set of measurements for each eye; when this was the case, the order of testing was good eye, bad eye, bad eye, good eye. The good eye was defined

as the eye with the better Snellen acuity. Subjects were rested between each experimental run. The eye not used was occluded with translucent diffusing paper. We chose not to use an eye patch since in preliminary work with some patients we found that this resulted in temporary monocular diplopia in the occluded eye: this could seriously contaminate contrast sensitivity measures (*see* Apkarian *et al.*, 1987; Travis *et al.*, 1987).

We used the Method of Adjustment to collect the threshold measurements since we have found this to be most efficient with our patients' time. One of 20 gratings was selected randomly by the computer. The grating was one of 5 spatial (1, 2, 4, 8 and 16 c/deg) and 4 temporal (0, 1, 4 and 16 Hz) frequencies. The selected grating was then presented to the subject at a contrast of 7.7%. The subject, using a response box, was able to raise or lower the contrast of this grating in 2 dB steps until it was at detection threshold, and this contrast was recorded. Our subjects were instructed to regard threshold as the contrast at which they could just determine that they were not looking at a uniform blank screen. The next grating was then presented according to the predetermined random sequence. When modulated in time, successive gratings were drifted right or left alternately. There was no time limit set for completion of a threshold setting, but subjects were advised not to agonize over their decision. With this method we found that all of our subjects were able to set thresholds with accuracy, repeatability and speed: a complete spatiotemporal contrast sensitivity function could be obtained in under 10 min. In these experiments the temporal modulation of a stimulus involved drifting it at constant velocity.

Colour vision measurements

Apparatus and stimuli

Colour vision was assessed with the Pickford-Nicolson anomaloscope (for full details of this instrument, *see* Pickford and Lakowski, 1960). We chose to use a commercially available instrument rather than a more sophisticated laboratory test in order that our results might be of some clinical usefulness. In this instrument, the subject views a circular translucent panel. The panel is divided such that the hue of the right half (the test field) is provided by the mixture of two primary lights. The hue of the left half (the standard field) is fixed. The coloured lights are produced by passing light from a tungsten source through glass filters. The dependent measures are the range of mixtures of the two primaries in the test field that the subject will accept as a match to the standard field, and the midpoint of this range. These are obtained from the dial setting on the anomaloscope that controls the mixture of the primaries (the dial on the instrument is marked off in arbitrary units from 0–82).

We chose to measure two equations: the Rayleigh equation (i.e., a mixture of red and green to match yellow) and the Engelking-Trendelenburg equation (i.e., a mixture of blue and green to match blue/green). We use the first as an estimate of the red/green colour deficit (i.e., the extent of protanopia or deuteranopia) and the second as an estimate of the blue/green colour deficit (i.e., the extent of tritanopia). Ideally, the primaries in both cases should lie on dichromatic confusion lines so that, for the respective dichromats, the full matching range will be indistinguishable from the standard; in the Pickford-Nicolson anomaloscope the primaries lie close to, but not on, these theoretical confusion lines (*see* Pokorny *et al.*, 1979, pp. 106–110). However, we have confirmed that both kinds of congenital red-green dichromat will accept the full range of red/green mixtures on our instrument; we have so far been unable to test any tritanopes.

Procedure

Subjects sat 1 m from the screen. At this distance, the circular stimulus subtended 1.43° of visual angle. Viewing was monocular, through natural pupils, and both eyes were tested. Fixation was not constrained. The Rayleigh equation was always measured first. Each eye was tested once only on each equation, and the order of the tests was as for contrast sensitivity testing.

The testing procedure was carried out according to the instruction manual (Pickford and Lakowski, 1960). The experimenter first found a mixture of the two primaries in the test field that

the subject would accept as a match to the standard; and next explored the end points of this match. The dial readings at these end points were then noted.

RESULTS

Contrast sensitivity measurements

Of the 18 patients, 12 had Snellen acuities of 6/6 or better in both eyes; a further 3 patients had acuities of 6/6 or better in one eye. Only 1 patient had both eyes with worse than 6/9 acuity.

Each patient's contrast sensitivity was measured at 5 spatial frequencies (1, 2, 4, 8 and 16 c/deg) at each of 4 temporal frequencies (0, 1, 4 and 16 Hz). Eleven patients showed a significant loss in one eye compared with the other ($P < 0.05$ on a two-tailed sign test). In the remaining 7 patients there was little to suggest any highly selective loss that might be swamped by analysing all 20 spatiotemporal conditions together. Fig. 1 shows in summary form the better eye on each of the 20 conditions for the 18 patients.

Characterizing the pattern of loss in individual patients is not easy as the data from single patients are not readily evaluated by statistical tests. However, we have

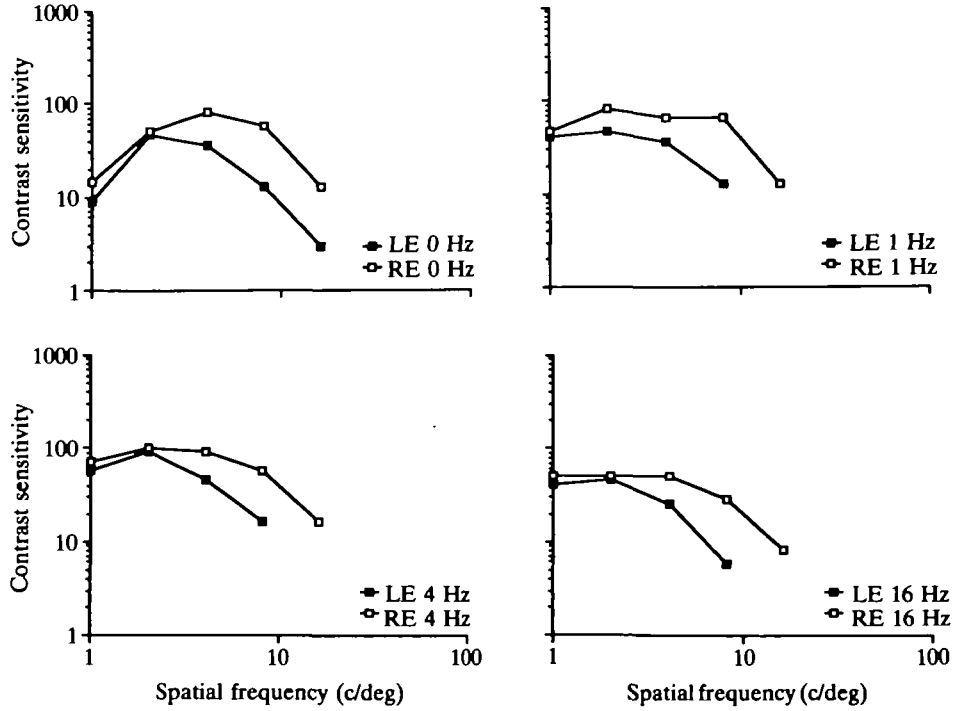

FIG. 1. Contrast sensitivity of *Case 18*. Filled squares show results for this patient's left eye, open squares for the right eye. Sensitivity (i.e. the reciprocal of the contrast, as a percentage, at threshold) is plotted against spatial frequency. Results are plotted separately for the four temporal frequencies.

TABLE 1. SPATIOTEMPORAL MAPS FOR 18 SUBJECTS WITH MS.

	Case 1				*Case 2*				*Case 3*			
	LE 6/5		*RE 6/5*		*LE 6/5^{-1}*		*RE 6/6^{-1}*		*LE 6/5^{-3}*		*RE 6/6^{-2}*	
16	R	R	R	L	R	R	L	L	L	L	L	
8	L	L	L	L	R	O	O	L	L	L	L	L
4	L	L	L	L	L	L	L	R	L	L	L	L
2	L	L	L	L	R	R	L	L	L	L	L	L
1	L	L	L	L	L	L	L	L	R	L	L	R
	0	1	4	16	0	1	4	16	0	1	4	16

	*Case 4**				*Case 5*				*Case 6*			
	LE 6/5		*RE 6/5*		*LE 6/5*		*RE 6/5^{-1}*		*LE 6/6*		*RE 6/6^{+4}*	
16	R	R	R	R	L	L	L	O	L	L	L	
8	L	R	R	R	O	R	O	R	R	R	L	R
4	R	L	R	L	R	O	O	R	R	L	L	L
2	R	R	L	R	R	L	L	R	R	L	O	R
1	L	R	R	R	O	R	R	R	R	R	L	R
	0	1	4	16	0	1	4	16	0	1	4	16

	Case 7				*Case 8**				*Case 9**			
	LE 6/9^{-1}		*RE 6/9^{-1}*		*LE 6/6^{-3}*		*RE 6/12^{+2}*		*LE 6/9^{+2}*		*RE 6/6^{+2}*	
16	L	R	L				L		R	L	R	R
8	R	R	R	L	L	L	L	L	R	R	R	R
4	R	R	R	R	L	L	L	L	O	R	O	R
2	R	L	L	R	L	L	L	L	R	L	R	R
1	R	L	L	R	R	L	L	L	R	R	O	R
	0	1	4	16	0	1	4	16	0	1	4	16

	*Case 10**				*Case 11*				*Case 12*			
	LE 6/12^{-1}		*RE 6/6^{+2}*		*LE 6/12*		*RE 6/18*		*LE 6/6*		*RE 6/6*	
16					R	L			R	R	O	R
8	R	R	R	R	L	L	L	L	L	O	R	R
4	O	R	R	R	L	L	L	L	R	O	L	R
2	R	R	R	R	L	L	R	R	R	O	R	O
1	L	L	R	R	L	L	R	R	L	L	R	L
	0	1	4	16	0	1	4	16	0	1	4	16

	*Case 13**				*Case 14**				*Case 15**			
	LE 6/9		*RE 6/24^{+1}*		*LE 6/5*		*RE 6/5*		*LE 6/6*		*RE 6/5*	
16	L	R	L	L	L	L	R	L	R	R	R	
8	L	L	L	L	L	L	L	L	R	R	R	R
4	L	L	L	L	L	L	L	L	R	R	R	R
2	L	L	R	L	L	L	O	R	L	R	R	L
1	R	R	O	L	L	R	O	O	O	L	L	R
	0	1	4	16	0	1	4	16	0	1	4	16

	Case 16				*Case 17**				*Case 18**			
	LE 6/5		*RE 6/5*		*LE 6/5^{-2}*		*RE 6/6^{-3}*		*LE 6/6^{+2}*		*RE 6/5*	
16	O	L	R		L	L	L	L	R	R	R	R
8	O	R	R	L	L	L	L	L	R	R	R	R
4	L	L	L	O	L	L	L	L	R	R	R	R
2	R	L	R	R	R	L	L	L	R	R	R	R
1	R	L	O	R	L	L	L	L	R	R	R	R
	0	1	4	16	0	1	4	16	0	1	4	16

Shown for each subject is the better eye (L = left, R = right, O = no difference) on the 20 spatiotemporal conditions. Each column corresponds to one of the four temporal frequencies; each row corresponds to one of the five spatial frequencies. For some subjects at the highest frequency, threshold measurements could not be obtained for either eye and hence these cells are left empty. Note that presenting the data in this simplified way conceals information about the magnitude of the difference at the different spatiotemporal points. An asterisk next to a subject number shows that the measured pattern of loss was significantly different from chance ($P < 0.05$).

no evidence for the narrowly-tuned spatial frequency losses reported by some researchers (e.g., Bodis-Wollner and Diamond, 1976; Regan *et al.*, 1981; Medjbeur and Tulunay-Keesey, 1985; Hess and Plant, 1986) and have found no evidence for narrowly-tuned losses in the temporal frequency domain. This latter result is unsurprising as it is now generally acknowledged that at each spatial frequency perhaps just two or three broad-band temporal channels exist (*see* Watson and Robson, 1981; Thompson, 1984; Anderson and Burr, 1985; Hess and Plant, 1985).

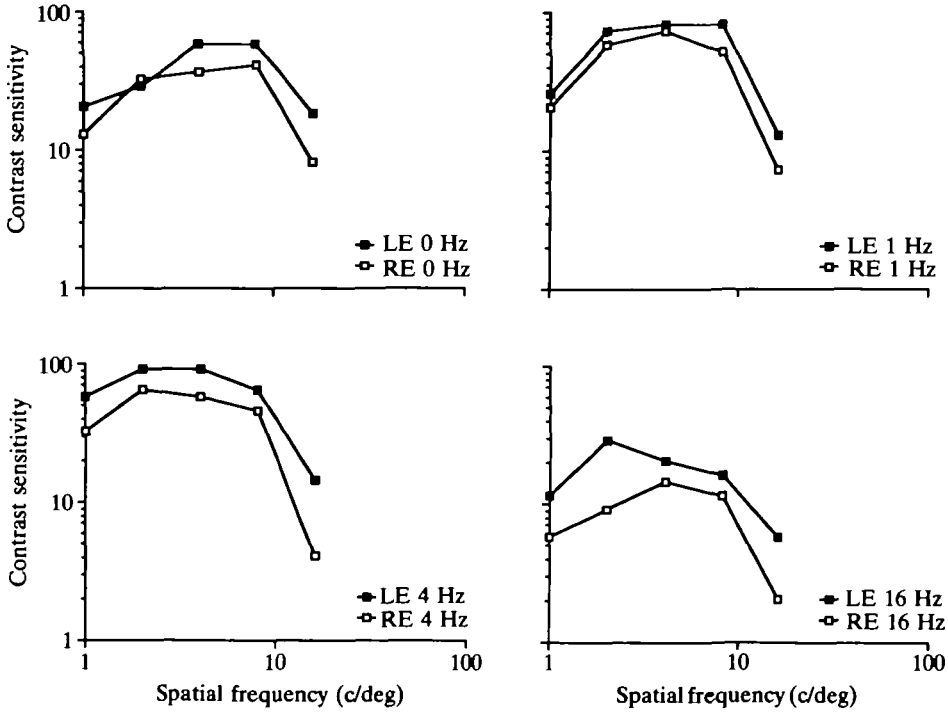

FIG. 2. Contrast sensitivity of *Case 17*. Details as fig. 1.

Of the 11 patients who showed significantly reduced sensitivity in one eye, 3 (Cases 4, 17, 18 in Table 1) appeared to suffer from a general loss at all spatial and temporal frequencies investigated, an example of which is seen in fig. 1. In 1 of these patients the loss appeared to increase quite markedly with increasing temporal frequency (*see* fig. 2). A further 3/11 patients (Cases 3, 8, 15 in Table 1) showed a similar pattern of loss but with little or no low spatial frequency loss.

Four of the 11 patients (Cases 3, 10, 13, 14 in Table 1) showed a different pattern of loss at low temporal frequencies than they did at high temporal frequencies. Fig. 3 illustrates 1 case where the contrast sensitivity loss between the two eyes disappeared with increasing temporal modulation and fig. 4 illustrates a case in which such a loss is revealed more reliably at high temporal frequencies.

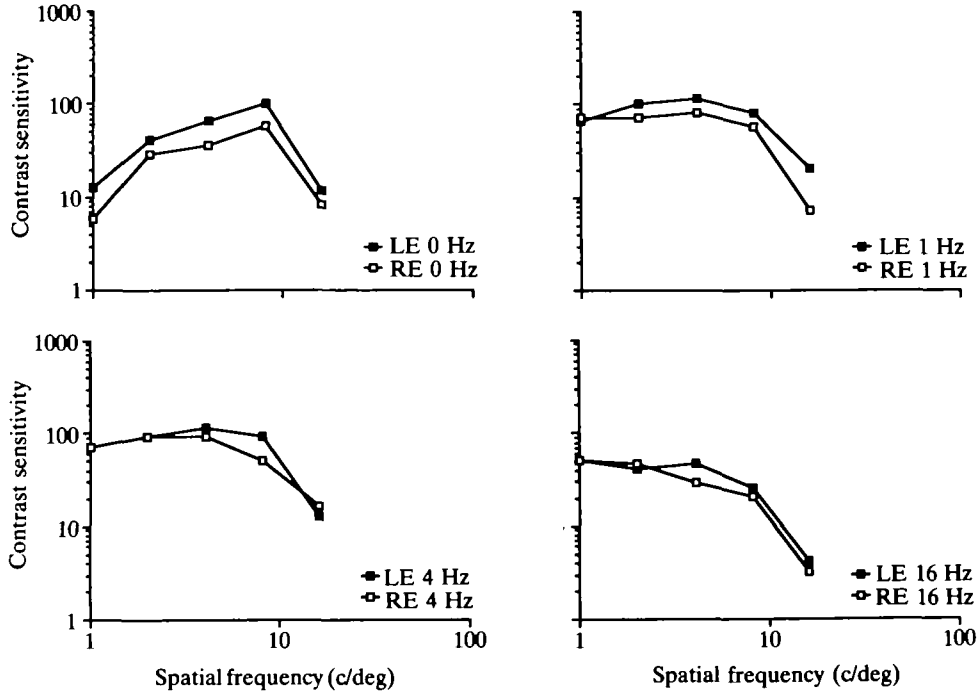

FIG. 3. Contrast sensitivity of *Case 14*. Details as fig. 2.

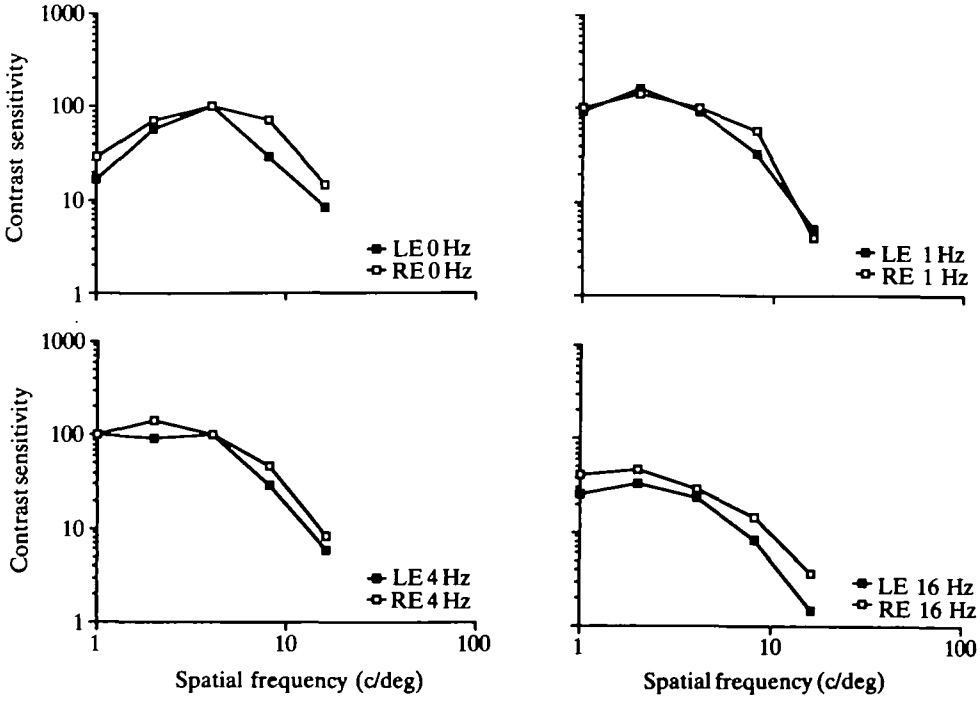

FIG. 4. Contrast sensitivity of *Case 9*. Details as fig. 2.

One patient (Case 1, fig. 1) showed a pattern of loss which deserves particular attention (*see* fig. 5). A small but highly reproducible relative loss in her right eye at low and medium spatial frequencies disappeared at high spatial frequencies where the left eye was less sensitive. This patient reported that the right eye was her 'bad' eye and yet could be shown to have higher acuity with that same eye.

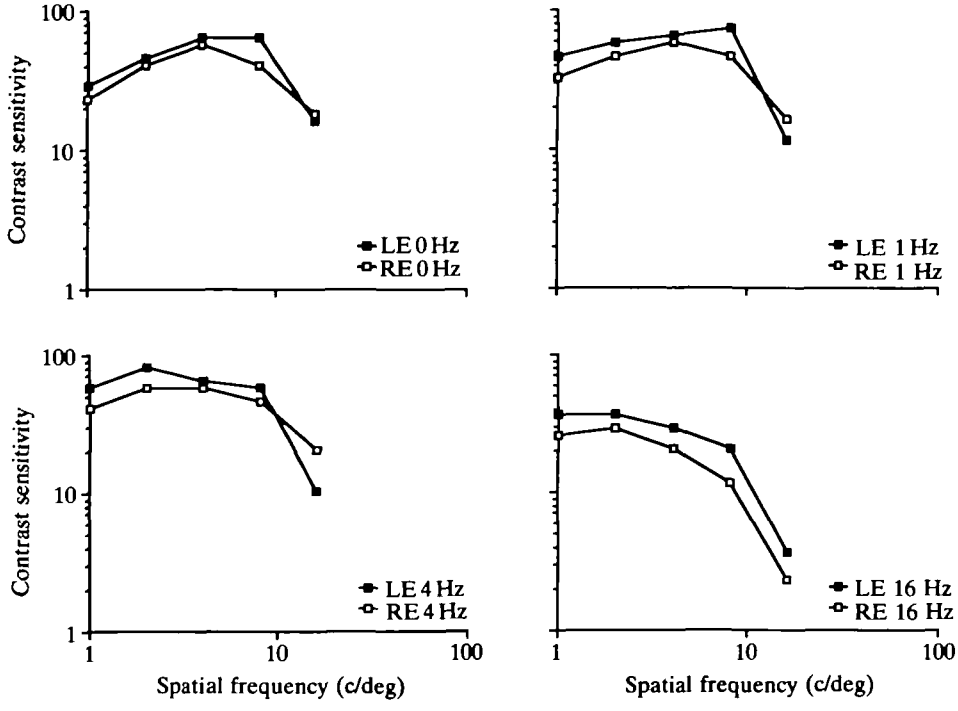

FIG. 5. Contrast sensitivity of *Case 1*. Details as fig. 2.

Colour vision measurements

When taken together, the data for the matching ranges on the Rayleigh and Engelking-Trendelenburg equations classify at least one eye of 15/18 (83%) of the patients as colour weak.

Results for each patient on the Rayleigh (red/green) equation are shown in fig. 6. Data for each eye are plotted separately. Plotted in the fig. is the range of red/green mixtures that the subject would accept as a match to the standard yellow. The larger, open symbol at the top of the fig. shows the mean setting ± 2.58 SD (99% confidence limits) for the group of control subjects. The mid-matching point (i.e., the centre of the matching range) for all but 3 patients (5 eyes) falls within 2.58 SD of the mean of the control group.

The subjects (Cases 3, 6, 8) who fell outside these limits were subsequently

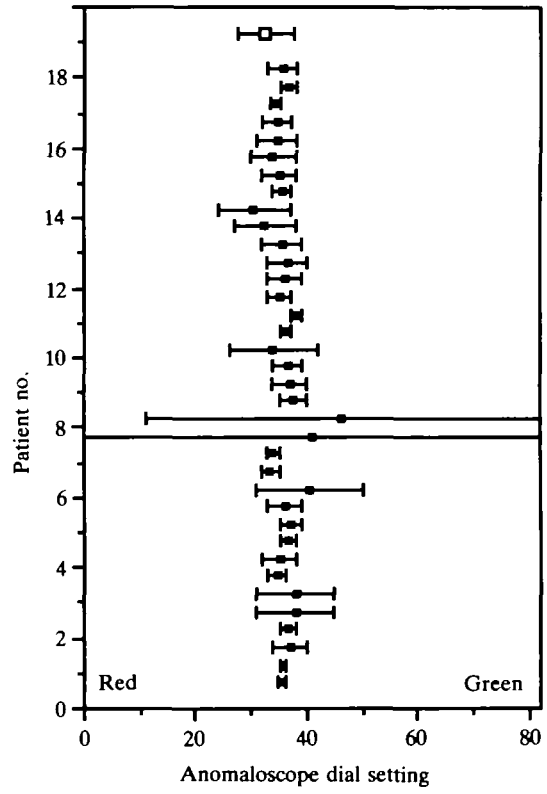

FIG. 6. Matching ranges and mid-matching points on the Rayleigh equation of 18 subjects with MS. The abscissa plots the scale setting of the anomaloscope: a value of 0 represents the most saturated red and 82 the most saturated green that the instrument could produce. Each filled symbol shows the mid-matching point for a particular subject; the associated bars show the range of settings that the subject would accept as a match to the standard yellow. The large open symbol at the top of the fig. shows the mean mid-matching point ± 2.58 SD of the control group. Results are shown for both eyes of each subject (the eye order from the bottom of the fig. upwards is right eye, left eye).

tested on the Ishihara test. Case 3 made three errors with her right eye but none with her left eye: given these results and that congenital red/green colour blindness is rare in females, her defect is probably acquired. Case 8, tested binocularly on the Ishihara test, made only one error; Case 6 made many errors with both eyes. These 2 patients were also tested on the Lanthony desaturated D-15 test and neither made any major errors (i.e., errors crossing the hue circle). Neither patient reported noticing any problems with his colour vision; indeed, Case 8 was an electrician before his illness and Case 6 claimed to have passed the Ishihara test while serving in the Armed Forces. Given that Case 6's deficit on the anomaloscope was monocular and that unilateral colour blindness is rare, we favour the hypothesis that his colour defect was acquired. We are unable to make a firm decision on Case 8; but given that he passed the Ishihara test for congenital colour blindness we tentatively suggest his defect is also acquired. Although there

are reports (e.g., Tokuda and Yasuma, 1983) of subjects who make errors on pseudoisochromatic plates yet have a normal Rayleigh match (Pigmentfarben-anomalie), it surprised us to find the converse: a subject who could pass the Ishihara test while being diagnosed as virtually dichromatic on the anomaloscope.

Although the midpoints for most of the subjects are within normal limits (defined as within 2.58 SD of the mean) on this test, in 34/36 eyes the mid-matching point is shifted towards green compared to the control group. This means that in general the MS patients required more green in the red/green mixture than the control group. A Mann-Whitney test comparing the patient's 'good' eye (defined arbitrarily as that eye having the mid-matching point closest to the mean of the control group) with the control group shows that the two groups are very significantly different from each other ($P < 0.0001$, two-tailed). Therefore, compared with control subjects, the settings of the MS patients on the Rayleigh equation are significantly deuteranomalous (*see* Discussion).

A second point of interest is the width of the matching range of the patients. As fig. 6 shows, 1 patient (Case 8) would accept the full range of 82 scale units with his worse eye. Pickford and Lakowski (1960) recommend that subjects whose matching range is about two or more times the normal *modal* range be defined as 'colour weak'. The modal range for the control subjects was four scale units. If we take twice the modal range as our definition of colour weak this defines 6 subjects (9 eyes) as abnormal (*see* Table 2). This includes the 3 subjects who had the anomalous midpoints. The numbers in the Table represent the ratio of the patient's range to the modal control group range; so a value of 2.0 or above is 'colour weak' using our criterion.

Do patients with MS in general accept a larger matching range than control subjects? This hypothesis was tested with a Mann-Whitney test. However, there was no significant difference between the matching ranges of the control group and either the patients' 'good' or 'bad' eyes, the 'good' eye being defined as that eye with the smaller range of settings ($P > 0.05$, two-tailed, in both cases). This is an important result because it means that the deuteranomalous shift in the midpoint in MS is not simply associated with a larger matching range. Colour discrimination can still be acute (*see*, e.g., the very small matching range of Case 1). In this regard, many of the patients in fig. 6 resemble mild deuteranomalous trichromats (but *see* Discussion).

Results for the Engelking-Trendelenburg (blue/green) equation are shown in fig. 8. As in fig. 6, the range of mixture settings that the patient would accept as a match to the standard are compared with a control group mean (± 2.58 SD). In this figure, the mid-matching points for the patient group all fall within the normal limits. Patient S9, who accepted a relatively small range on the Rayleigh equation, here accepted the full range of blue/green mixtures with both eyes. This subject passed the Farnsworth F2 plate for congenital tritanopia. Two of the cases (6 and 8) who fell outside of the normal limits on the Rayleigh equation did not take part in this experiment.

TABLE 2. MATCHING RANGES OF THE PATIENTS ON THE TWO EQUATIONS DIVIDED BY THE MODAL MATCHING RANGE OF THE CONTROL GROUP ON THE SAME EQUATION*

Case		*Red-green range/ modal red-green range*	*Blue-green range/ modal blue-green range*
1	RE	0.38	0.19
	LE	0.25	0.5
2	RE	1.5	7.5
	LE	0.75	7.0
3	RE	3.75	10.25
	LE	3.75	9.13
4	RE	0.75	7.5
	LE	0.75	3.0
5	RE	0.75	0.19
	LE	1.5	2.5
6	RE	1.5	
	LE	4.75	
7	RE	0.75	1.88
	LE	0.5	0.63
8	RE	20.5	
	LE	17.75	
9	RE	1.25	10.25
	LE	1.5	10.25
10	RE	1.25	1.88
	LE	4.0	2.25
11	RE	0.5	2.5
	LE	0.5	2.0
12	RE	1.0	1.38
	LE	1.5	2.0
13	RE	1.75	4.0
	LE	1.75	7.13
14	RE	2.75	1.25
	LE	3.25	1.13
15	RE	0.75	2.88
	LE	1.5	4.5
16	RE	2.0	1.38
	LE	1.75	1.13
18	RE	0.75	2.63
	LE	1.25	2.63

* A value of unity would show that the patient had the same matching range as the control group mode; a value of 2.0 or above may be considered colour weak. RE = right eye; LE = left eye.

Unlike the results for the red/green equation, the mid-matching points for the patient group do not appear to lie systematically on one side of the mean for the control group. Indeed Mann-Whitney tests comparing the mid-matching points of the control group with the patients' 'good' and 'bad' eyes (defined as above) were not significant ($P > 0.05$, two-tailed). Moreover, a Mann-Whitney test showed there is no significant difference between the matching ranges of the patients 'good' and 'bad' eyes and the matching ranges of the subjects in the

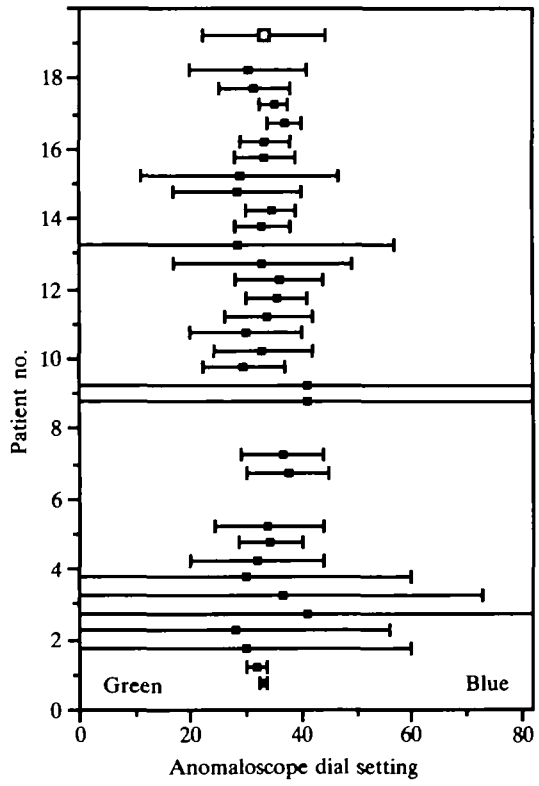

FIG. 7. Matching ranges and mid-matching points on the Engelking-Trendelenburg equation of 16 subjects with MS. The abscissa plots the scale setting of the anomaloscope: a value of 0 represents the most saturated green and 82 the most saturated blue that the instrument could produce. Other details as fig. 7.

control group ('good' eye defined as that eye with the smaller matching range, $P > 0.05$, two-tailed in both cases). However, the modal range for the control group was 8 scale units; more than half of the patients (11/18, 61%) have matching ranges for at least one eye greater than 2.0 times this value (*see* Table 2). Given that congenital tritanopia is so rare we favour the hypothesis that the colour defect in these patients is acquired.

Of the 4 patients who both performed abnormally on the Rayleigh equation and also performed the Engelking-Trendelenburg equation, 2 were shown to be defective on both tests.

Comparison of contrast sensitivity and colour vision measurements

As outlined in the Introduction, it has been proposed that the L-M cells in the lateral geniculate nucleus could perform two tasks, multiplexing information on both the chromatic and spatial attributes of a stimulus. If a demyelinating lesion should disrupt communication between the retina and the lateral geniculate we can predict that performance on the Rayleigh equation should broadly correlate

with performance on the spatiotemporal task. However, as the parvocellular units that receive opposed inputs from short-wave cones and some combination of long and middle-wave cones (S-(L and M) cells) are relatively unimportant for spatial vision, we can predict that performance on the Engelking-Trendelenburg equation should not correlate with performance on the spatiotemporal task.

We decided to specify the contrast sensitivity deficit at any particular point in spatiotemporal space by differencing the threshold contrast sensitivities (in dB) of the left and right eyes. Similarly, the colour vision deficit was specified by differencing the range settings (in scale units) of the left and right eyes. It should be stressed that this procedure was not to classify either a colour or spatial frequency deficit but to provide an index of the relative degree of damage between the two eyes.

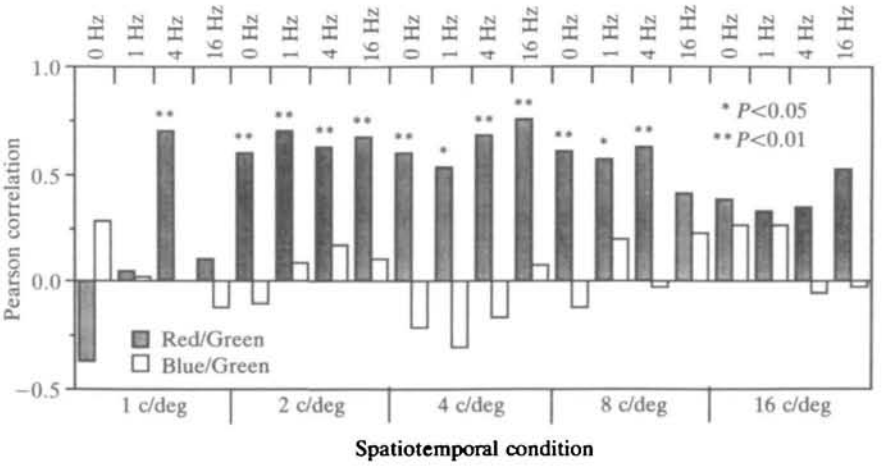

FIG. 8. Histogram of the Pearson correlations between colour deficit and contrast sensitivity deficit. The colour deficit was defined as the difference between the eyes in the range settings measured in scale units. The contrast sensitivity deficit for a particular spatiotemporal point was defined as the difference between the eyes in contrast threshold measured in dB. A single asterisk denotes a correlation significant at the 95% confidence level and a double asterisk significance at the 99% level (both two-tailed). At the higher spatial frequencies, the contrast thresholds of some subjects corresponded to contrasts of 77% and above (a nonlinear range on our screen) and so were discarded from this analysis; hence the sample size differs in different conditions. For the red/green equation, n = 18 except for the following spatiotemporal conditions: 1 c/deg, 16 Hz (n = 17), 2 c/deg, 4 Hz (n = 17; 8 c/deg, 16 Hz (n = 17); 16 c/deg, 0 Hz (n = 16); 16 c/deg, 1 Hz (n = 14); 16 c/deg, 4 Hz (n = 15); 16 c/deg, 16 Hz (n = 8). For the blue/green equation, on which 2 of the subjects were not tested, n is 2 less than the sample size for the red/green equation for each corresponding spatiotemporal condition.

With only one exception, all of the correlations with the differences between the range settings on the Rayleigh equation and the differences between the threshold contrast sensitivities at a particular spatial and temporal frequency are higher than the analogous correlations for the Engelking-Trendelenburg equation. The histogram in fig. 8 shows the results. Along the abscissa is plotted the particular spatiotemporal condition; the ordinate plots the Pearson correlation

coefficient. None of the correlations between the range difference on the Engelking-Trendelenburg equation and the threshold difference at a particular spatiotemporal point is statistically significant ($P > 0.05$); more than half (12/20) of the analogous correlations for the Rayleigh equation are (the figure gives the confidence intervals).

With only one exception, however, the correlations with the red/green colour deficit are not significantly different from chance at the very lowest and highest spatial frequencies. These conditions that do not provide a strong correlation are not unexpected. The inability of a number of subjects to detect any gratings of the highest spatial frequency may account for the lack of significant correlations with the red/green colour deficit at 16 c/deg. At the lowest spatial frequency where three of the four correlations are not significantly different from chance, the magnocellular cells may provide a suitable achromatic pathway for detection of these gratings and hence a strong correlation with the red/green colour deficit would not be expected. The implication of these correlations is that in MS, colour discrimination losses that depend on L-M cells are associated with contrast sensitivity losses, whereas colour discrimination losses that depend on S-(L and M) cells are not.

DISCUSSION

The main findings of this study are (1) that MS causes varied spatiotemporal contrast sensitivity losses; (2) that MS causes acquired red/green and blue/green colour vision deficits; and (3) that the red/green colour deficit correlates strongly and positively with contrast sensitivity loss whereas the blue/green colour deficit does not.

With regard to the contrast sensitivity measures, we should point out that by making inter-eye comparisons rather than comparisons with a control group we do not make the assumption that our subjects have one entirely normal eye. Such an assumption would indeed be a difficult one to support. This is because both optic nerves are often damaged in MS. For example, Ulrich and Groebke-Lorenz (1983) examined histologically both optic nerves in 18 cases of MS; only one of the 36 optic nerves showed no evidence of demyelination, and yet in only 8 of the 18 patients had a diagnosis of unilateral or bilateral optic neuritis been reported. Our assumption in the present study is merely that the contrast sensitivity loss is greater in one eye than in the other.

With this caveat in mind, our results conflict with those of Brussell *et al.* (1984) who found that temporal modulation had no effect on the stationary contrast sensitivity functions for their patients. We believe this is because the patients in their study were instructed to make eye movements (Brussell *et al.*, 1984, p. 302); this of course makes it impossible to specify the temporal frequency of the gratings and could even nullify the effects of temporal modulation. This is supported by their own fig. 1 which shows little or no difference between the contrast sensitivity functions for stationary and moving gratings. It is well established that the band-

pass characteristic of the contrast sensitivity function measured with stationary gratings becomes low-pass with temporally modulated gratings (Robson, 1966). In some of our patients we observed the pattern of results described by Hess and Plant (1985), that is, a decrease in the deficit with increasing temporal frequency, but for gratings of low spatial frequency only. It is intriguing to note that this pattern of loss would fit a selective loss in the parvocellular pathways.

One reason why we may not have found more exemplars of Hess and Plant's condition is because their measurements extended to spatial frequencies as low as 0.2 c/deg, whereas ours began at 1 c/deg. The nature of the contrast sensitivity losses that we observed are closest in agreement to those of Medjbeur and Tulunay-Keesey (1985), who demonstrated a number of temporal and spatial contrast sensitivity losses in patients with optic neuritis and MS. We believe that an explanation for these results may lie partly in the fact that demyelinating lesions of variable severity appear to be placed randomly within the anterior visual pathway (Ulrich and Groebke-Lorenz, 1983).

Part of our second result, that MS may cause a red/green colour deficit (6/18 patients), is consistent with the work of Cox (1961), whose study has been marshalled to support the hypothesis that optic nerve damage leads to an acquired type II colour vision deficit. Support for the notion that MS may be associated with some 'pseudo-deuteranomaly' comes from Grützner (1966) and Marré and Marré (1986). Verriest (1963) also reports anomaloscope matches to be deuteranomalous in optic neuritis, although the effect is described as 'a general enlargement of the matching range without a clear shift to the green' (cited in Foster, 1986, p. 163). Nagel (1905, cited in Pokorny and Smith, 1986) also described a red/green colour defect in optic neuritis. The subtle shift of the Rayleigh match to the green that we found in our patients taken as a group was not associated with an enlarged matching range and we emphasize that the mid-matching points of the great majority of our patients fall within normal limits on this test. Indeed, the existence of the shift might be treated with some caution since between testing the patient and control groups we were obliged to replace the anomaloscope bulb; however, the evidence that we have been able to gather does not reveal any systematic change in the calibration of our instrument. Furthermore the experimental and control groups were run at different times of the year and seasonal variations in anomaloscope measures have been reported (e.g., Richter 1948; Boles-Carenini, 1954).

Two of the patients tested were shown to be abnormal on both the Rayleigh and Engelking-Trendelenburg equation, consistent with a severe type II acquired defect. A majority (11/18 patients) had matching ranges on the Engelking-Trendelenburg equation that betray a type III (tritan-like) deficit, although the mid-matching points for all our patients on this equation are within normal limits. This type of deficit has been reported in many diseases of the eye, as well as systemic diseases (Pokorny *et al.*, 1979). However, it is not generally considered to be symptomatic of MS or optic nerve damage unless it occurs in conjunction

with a red/green loss (and would hence be categorized as a severe type II loss). This defect has also been reported in some patients (2/5) with retrobulbar neuritis by Ohta (1970) using the Farnsworth Panel D-15. Other reports of tritan-like deficits have been reported by experimenters using the Lanthony D-15 test (most recently, Fredriksen *et al.*, 1986). The type III defect may be caused by a lesion to any point along the visual pathway (Pokorny *et al.*, 1979, p. 80).

It should be made explicit that, as with the contrast sensitivity measures, we cannot classify the colour vision deficit in MS in any general terms. Some individual patients show a type II acquired defect and others a type III. We suspect that this is because the demyelinating lesions in MS are not restricted simply to the optic nerve, damage to which is generally thought to be the cause of type II acquired defects, but may occur at any point along the visual pathway. Furthermore, Kirshner *et al.* (1985) provided MRI evidence for scattered cerebral lesions in 35/35 patients with MS (definite, probable and possible cases). Ormerod *et al.* (1986) have recently demonstrated such lesions in patients presenting with optic neuritis. In our patients, with long-standing MS, a plaque of demyelination in the visual cortex might produce a number of perceptual difficulties that, in the interests of parsimony, most workers might ascribe to optic nerve damage. What is clearly required at some future date are MRI, contrast sensitivity and anomaloscope data on the same patients with MS in order to produce a correlative study between the type of visual defect and the site of the demyelinating lesions. We would predict that those patients with type II acquired colour vision deficits would have lesions confined predominantly to the optic nerve; those with type III acquired defects would have lesions at different or additional sites along the visual pathway.

Although the 'double-duty' cells reported by Derrington *et al.* (1984) were found in the lateral geniculate nucleus of their animals, the striking correlations that we have found between red/green colour vision and contrast sensitivity performance need not necessarily implicate plaques of demyelination in this region in our patients. A more parsimonious conclusion would be that the optic nerve fibres providing input to the appropriate cells have been damaged by the disease. Once again we do not propose that this demyelination is selective; indeed, the very fact that blue/green colour vision is also disrupted in our patients argues against such a conclusion. Instead, our conclusion is that the varied spatiotemporal contrast sensitivity and colour vision deficits in MS that have been reported in the literature are likely to reflect damage to the same cells in the visual pathway. If these cells perform 'double-duty', then our results are consistent with a model of random demyelination at many points along the visual pathways, including the optic nerves, tracts and radiations, rather than selective or more disruptive damage to fibres carrying information about colour (Fallowfield and Krauskopf, 1984) or luminance (Zisman *et al.*, 1978).

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