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COLOR VISION LOSSES IN MULTIPLE SCLEROSIS

by

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ABSTRACT

The diagnosis of multiple sclerosis (M.S.) is dependent upon objective evidence of lesions in anatomically distinct parts of the central nervous system. Although autopsy studies indicate a predilection for plaques of demyelination in the visual system of patients with M.S., disturbances of visual function may not be clinically detectable with conventional tests such as the Snellen visual acuity chart. This study was undertaken to investigate whether color vision tests might be useful in evaluating visual function in patients with M.S.

A battery of color vision tests was employed, including: A) pseudoisochromatic screening tests; B) the Farnsworth-Munsell 100-Hue (FM 100-Hue) test, a full spectrum, hue discrimination test; and C) the Pickford-Nicolson (P.N.) anomaloscope, a modified colorimeter. Various criteria were considered to establish pass/fail standards for the tests used. A careful qualitative and quantitative analysis was made of the color losses which occurred.

Color deficits were found in 45% of patients tested with the Ishihara Plates, 50% of patients tested with the FM 100-Hue test, and 70% of patients tested on the anomaloscope. Results from the various indices of visual function were compared. There was a statistically significant correlation between an abnormal VEP latency and optic neuritis which substantiated the diagnosis of optic neuritis. However,

there was not a significant correlation between an abnormal VEP latency and a 'blue' color vision deficit. It was hypothesized that this may be because the two tests assess different physiological functions or channels. The lack of a significant correlation between optic neuritis and 'blue' color vision defects led to speculations that post-chiasmal lesions may contribute to color vision losses in M.S. patients. There was a generalized reduction in wavelength discrimination particularly in the blue area of the spectrum which might be interpreted as a disturbance in the opponent processing of chromatic information in M.S. patients.

The results of this study suggest that color vision testing might be a useful option to consider in the investigation of M.S. patients, even if there are no other clinical signs of visual system involvement.

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DEDICATION

Dedicated to my loving and beloved family.

Thank you

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I. INTRODUCTION

1.1 INTRODUCTION

Multiple sclerosis (M.S.) is a multi-focal, demyelinating disease of the central nervous system, usually characterized by a remitting-relapsing course, with impairment of function in multiple neural pathways. The visual system appears to be particularly vulnerable to the effects of M.S. This is reflected not only by the large number of patients who have visual symptoms (McAlpine, Lumsden and Acheson 1965) but also, and perhaps more significantly, by histological evidence of plaques in the visual system of all M.S. patients examined during an autopsy study (Lumsden 1970). It appears that structural and functional abnormalities may be present in M.S. patients even in the absence of visual symptoms (Gartner 1953; Halliday, McDonald and Mushin 1977). Since the diagnosis of multiple sclerosis is dependent upon the demonstration of lesions in more than one site in the central nervous system, tests which can objectively document visual symptoms or demonstrate subclinical visual impairment may be extremely useful in assisting the clinical diagnosis and evaluating the progress of the disease.

The studies reported here were conducted to determine whether color vision tests might be useful in evaluating visual function in patients with multiple sclerosis. In addition to this fundamental concern, other questions relevant to the issue of color vision losses

in M.S. were also considered. What clinically appropriate methods of testing and analysis of results can be used to demonstrate color vision losses? What types of color vision capabilities and what areas of the spectrum are affected? How do these losses relate to, or compare with, other indices of visual function? Do these losses imply anything about multiple sclerosis, for example, the possible anatomical site of the lesions determined with clinical testing rather than at autopsy? Do these losses imply anything about fundamental mechanisms of vision or color vision?

This study is comprised of two parts. In the initial investigation 40 M.S. patients were selected based on records from the Calgary General Hospital (see Section 2.2.1). Investigation of these patients involved a neurological evaluation and an assessment of visual function with a variety of tests (see Section 2.2.2.) including a battery of standard color vision tests. The results of color vision testing were catalogued and compared with published norms and with results in an appropriate control population. The color vision test results were also correlated with other indicia of visual function. Ten patients were then retested as part of a further investigation with the Pickford-Nicolson anomaloscope. Data obtained from anomaloscope testing of the M.S. patients were compared with published norms for the instrument used, and with data obtained from anomaloscope testing in a population of patients with raised intraocular pressure. This comparison was considered relevant for a number of reasons.

1) Prolongation of the VEP latency can occur in M.S. patients

(Halliday, McDonald and Mushin 1972) and in glaucoma patients (Adams et al. 1982).

2) Losses in hue discrimination in the blue area of the spectrum occur in patients with M.S. (see Chapter 3) and in patients with glaucoma and ocular hypertension (Lakowksi, Bryett and Drance 1975; Lakowski and Drance 1979).

3) There is histological evidence of gliosis and glial cell damage to the optic nerve in M.S. patients (Lumsden 1970) and in patients with glaucoma (Duke Elder 1969, p. 434; Anderson 1972).

This introductory chapter provides background in three areas: multiple sclerosis, with particular reference to visual system affectation in the disease; color vision; and a review of literature relevant to color vision and visually evoked potentials. Chapters 2 and 3 are the Methods and Results sections respectively. Chapter 4, the Discussion, highlights aspects of the results I wished to emphasize. It also proposes possible hypotheses to account for the results, with a few suggestions for further investigation which might be undertaken to test these hypotheses.

1.2 MULTIPLE SCLEROSIS

1.2.1 Etiology

Multiple sclerosis (M.S.) is a diffuse demyelinating disease of the central nervous system, believed to be caused by a delayed immune response to a virus infection. The strongest evidence suggesting an infectious agent (or agents) in M.S. is the epidemiology of the disease. There are fairly well defined geographical locations of high, medium and low risk. The high risk areas occur in the temperate zones with predominately Caucasian populations. Migration studies suggest that the enhanced risk of acquiring M.S. might be established before the age of 15 years (Kurtzke 1980). "Epidemics" of M.S. occurred in the Faeroe Islands and in Iceland following occupation by British troops during World War Two.

Immunopathology also suggests an infectious etiology for the disease and implicates an immune-mediated mechanism. The high proportion of immunogobulin (Ig) G to the total amount of protein, and the presence of oligoclonal banding, suggests a primary response to either a persistent viral infection or a central nervous system (CNS) autoantigen. It appears that in M.S. IgG may actually be produced in the CNS, as well as in serum.

Antibodies to a variety of viruses, particularly measles (in 31 of 35 studies) (Cook and Dowling 1980), have been found in both serum and CSF of M.S. patients. However measles antibody titres also tended

to be elevated in siblings and controls in high-risk areas. IgM specific for measles or any other common virus has not been found. Increased levels of canine distemper virus (CDV) antibodies have also been found in several studies of M.S. patients. CDV is of particular interest since it is extremely neurotoxic in its natural host and can produce a range of symptoms in a variety of animals including primates. Although CDV has never been shown directly to cause disease in man, three "epidemics" of M.S. have been preceded by outbreaks of distemper in dogs. In the largest study demonstrating increased CDV antibodies in M.S. patients (Cook, Dowling and Russell 1979) most of the patients also had increased antibodies to measles. Since measles and CD viruses are antigenically similar, the possibility of cross-reactivity must be considered.

To investigate cell-mediated immunity in multiple sclerosis, lymphocyte reactivity in response to various viruses and proteins has been assessed. While there is a suggestion of increased in vitro lymphocyte reactivity to myelin basic protein in certain M.S. patients, many questions remain. As with experiments and data in the antibody-antigen reaction in M.S., there are many difficulties in establishing the specificity to M.S. and the mechanics of the reaction.

A possible immunogenetic aspect to M.S. is also being investigated. Certain HLA histocompatability antigens and cellular immunity markers are significantly more common in M.S. patients than in controls. However, the significance of this is not clear. Does this

represent a genetic susceptibility to the disease, a receptor for the virus, or an unrelated secondary effect (Poser in Merrit 1979; Lisak 1980)?

Although the epidemiology suggests an infectious agent, and the serological findings suggest an immune response, attempts to clearly demonstrate an infectious etiology for M.S. patients have not been successful. Numerous attempts have been made to isolate a virus from M.S. tissue, to transmit the disease to animals by innoculation of M.S. tissue, and to identify viral structures or antigens in M.S. tissue. However, these studies have yielded no definitive evidence that any single virus or viral agent can cause M.S. A number of explanations are possible to account for the absence of a direct, unequivocal link between M.S. and prior infection by any of the commonly occurring viruses.

1. The seriological findings could be the result of a generalized increase in immune responsiveness (which might be either causative or secondary to the M.S. process) (Cook, Dowling and Russell 1979).
2. An as yet unidentified virus may be reponsible.
3. It may be the inter-relationship between multiple infectious agents, rather than a single virus that triggers M.S. This is thought to be the case with Guillain-Barré syndrome, another human demyelinating disease (Cook and Dowling 1980).
4. There appears to be a very delicate and complex relationship between subsets of cells and their products which maintains the

normal balance between humoral and cell-mediated immune responses. It may be that M.S. is not the result of a hidden antigen but an abnormality in the inter-relationship of these normal mechanisms (Lisak 1980).

5. If the CNS lesions were due to an autoimmune response, the virus which triggered it might no longer be present when the response occurs.

1.2.2 Pathology

M.S. is characterized by multiple focal lesions. In the affected region there is loss of myelin and oligodendrocytes with proliferation of astrocytes, microglia and plasma cells. There is usually relative sparing of axons although in advanced cases of the disease there may be some axonal damage as well (McKhann 1982). The demyelinated lesions are flanked by histologically normal neural tissue. Experimental evidence (MacDonald 1977) indicates that although large areas of demyelination result in complete blockage of nervous transmission, smaller sections of demyelination merely cause a prolongation of the refractory period and slowing of conduction. This is in contrast to axonal degeneration, in which conduction is totally blocked once degeneration begins.

The course of M.S. is characterized by acute exacerbations in which there may be severe impairment of the affected neurological system. Early in the disease, in most cases this is followed by

remission with functional recovery to normal or nearly normal levels. In many instances this recovery is too rapid to be due to remyelination, if indeed remyelination is possible. Pathological evidence suggests that the majority of axons remain demyelinated, with remyelination limited to the periphery of the lesion (Prineas and Connell 1978).

A number of hypotheses have been formulated to account for the remitting, relapsing nature of M.S. and the occurrence of transient symptoms. These include:

1) The repeated attacks may be related to a nonspecific immunological challenge or to antigenic shifts of the latent transmissable agent (McKhann 1982);
2) The inital impairment of function during an acute attack may be due to a local inflammatory response. Once this response has subsided function may be restored;
3) Recovery of conduction in persistently demyelinated areas may be related to the spread of sodium channels along the nerve from their normal locations at internodes (McKhann 1982);
4) Demyelination reduces the 'margin of safety' or functional reserve for transmission of nervous impulses. Physiological alteration of conduction capacity (e.g. by raising body temperature) may result in transient clinical symptoms by exceeding the reduced self-regulatory capacity of nerve fibres (Posner in Merritt 1979);
5) Synaptic transmission might be impaired by antibody mediated

inhibition of transmitter release. This type of 'blocking factor' has been found in the serum of some M.S. patients (Schauf et al. 1981).

1.2.3 Diagnosis and Treatment

The diagnosis of M.S. is a clinical one based upon objective indications of lesions in two or more separate sites in the white matter of the central nervous system in the absence of a satisfactory alternative explanation for the observed abnormalities (McDonald and Halliday 1977). Most patients have a relapsing, remitting course initially which is classified as clinically definite, probable or suspected. Although the majority of patients do not seem to have a progressive course until late in the disease, about 10 percent demonstrate a progressive course from the beginning. In both presentations of the disease the diagnostic category is a function of the number of neurological sites or neural systems implicated, the number or type of previous episodes, and the exclusion of other possible causes of the symptoms (see Appendix Table A.1 for McDonald and Halliday Classification used by the Calgary Multiple Sclerosis Clinic).

Although steroids appear to improve neurological function in some patients during acute relapses, they do not affect the progression of the disease (Ellison and Myers 1980). There is no consistently applied clearly effective treatment for M.S. at present.

Laboratory tests are useful for confirming the clinical diagno-

sis and demonstrating the existence of asymptomatic lesions, but there is no specific test for M.S. The most commonly used tests include: the analysis of CSF to determine the proportion and type of IgG present; evoked potentials to visual, auditory and/or somatosensory stimuli; and a myelogram to rule out a compressive spinal tumor.

1.2.4 Visual System Involvement

Demyelination of the optic nerve is a common early feature of multiple sclerosis (Halliday, McDonald and Mushin, 1972). In the acute phase, if the optic nerve head is affected, diagnosis may be made by the appearance of the disc, in addition to the patient's signs and symptoms. However, it may be difficult to make a retrospective diagnosis particularly in cases of retrobulbar (behind the eyeball) neuritis. Assessing the paleness of an optic disc to determine the presence of optic atrophy is a very subjective (and at times difficult) evaluation by the examiner. Therefore tests which can objectively document impairment of visual function in cases of suspected optic neuritis are extremely valuable in confirming the diagnosis. Of even greater significance is the objective documentation of visual system involvement in patients without any signs, symptoms or history of optic neuritis. In the following paragraphs I discuss a few tests designed to assess specific spatial or temporal aspects of visual function shown to be affected in multiple sclerosis. These include an electrophysiological technique (the VEP) and selected psychophysical techniques. I

have not included tests which are part of the standard ophthalmalogical examination such as visual acuity, visual fields or pupillary reaction.

Visually Evoked Potentials

The visually evoked potential is a non-invasive electrophysiological technique representing the summed electrical activity of groups of neurons recorded by scalp electrodes in response to a visual stimulus. Since the visually evoked potential is small compared with the overall electroencephalographic activity, responses from a succession of stimuli are averaged to produce a characteristic wave form. Transient VEPs are produced in response to slow temporal frequencies (typically 1-2 Hz). The individual EEG waves which result are usually recorded with scalp electrodes over the occipital cortex. A fairly large number of these waves are averaged, typically 100 stimulus repetitions, and the averaged waveform is then assessed. Steady-state VEPs are generated by repetitive stimulation at high temporal frequencies (10-60 Hz). This results in a long train of identical waveforms that repeat themselves at the stimulus repetition frequency.

At present the VEP technique most commonly employed for clinical testing is a transient VEP with a pattern stimulus. A reversing checkerboard pattern in which the black and white checks trade position is utilized to maintain a constant overall luminance. The criterion used to establish a visually evoked waveform as being normal is the value of the latency between the time of stimulus presentation and the

first major positive peak, called P_1 or P_{100}. Small checks (under 30' of arc) appear to stimulate foveal vision whereas larger checks (greater than 50' of arc) seem to stimulate peripheral vision (Harter, 1970). The VEP to larger or smaller checks may have somewhat greater amplitude depending on the retinal region stimulated but the waveform and latency seem to be the same in both cases (Asselman, Chadwick and Marsden, 1975). In clinical practice various authors have utilized checks of various sizes, 15.5' to 50' of arc, with similar results. Once local pathology is excluded, a delay in the latency of the pattern-reversed VEP is the most reliable index of optic nerve pathology (Celesia, 1978). The delay is not specific to M.S. but does occur in a usefully high percentage of M.S. patients: 96%[1] - 67%[2] overall; 100%[1,2] with optic neuritis (88%[2] with optic atrophy); 93%[1] - 28%[2] clinically normal. This last finding of M.S. patients with clinically normal eyes who demonstrated a prolonged VEP latency is especially useful for aiding the diagnosis of M.S. by detecting clinically silent lesions.

Psychophysical Techniques

Psychophysics is the "science of relations between mental and physical phenomena" (Funk and Wagnall, 1977). Unlike electrophysio-

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1 Halliday, McDonald and Mushin, 1977.

2 Asselman, Chadwick and Marsden, 1975.

logical techniques in which neural responses can be objectively measured by a recorded waveform, psychophysical techniques require a conscious response from the subject. Psychophysical techniques, like electrophysiological methods, can be used to demonstrate temporal abnormalities in the processing of information. It has been known for some time that critical flicker fusion frequency (the temporal frequency at which a train of flashes will appear to fuse into a single constant light) is reduced in a high percentage of M.S. patients, particularly in patients with optic atrophy (Titcombe and Willison, 1961). In addition, the time interval necessary between two brief flashes of light in order for them to be perceived as separate was impaired in 13 of 14 M.S. patients with retrobulbar neuritis (Galvin, Regan and Heron, 1976). This ability has been termed temporal resolution and is a different function from critical flicker fusion frequency (Boynton, 1979). Perceptual delays in appreciating an increase in light intensity may be demonstrated with 'delay campimetry' (Heron, Regan and Milner, 1974). The measured delays are relative - comparing different retinal sites in the same eye (i.e. foveal and peripheral) or the same retinal site in the right and left eyes. This technique confirmed the diagnosis of retrobulbar neuritis in all 22 M.S. patients tested, and revealed pathology in 12 of 19 M.S. patients with no history of retrobulbar neuritis (Regan, Milner and Heron, 1976).

As well as abnormalities in the temporal analysis of visual information in M.S. patients, there are also indications of deficits in the spatial analysis of information. With conventional visual acuity

testing it is often assumed a subject sees well if he can resolve the 20/20 line on a Snellen chart. However, this line is a high contrast target made up of high spatial frequencies. A more sensitive test of spatial vision is to assess the contrast threshold at which a particular spatial frequency is visible. This relationship of contrast sensitivity versus spatial frequency may be displayed as a modulation transfer function with sensitivity losses charted as a "difference curve" (Regan, Silver and Murray, 1977) or as a visuogram (Bodis-Wollner et al., 1979). Regan, Silver and Murray (1977) found that 20 of 48 M.S. patients demonstrated selective spatial frequency losses; 11 of the 20 had deficits in the mid range spatial frequencies. Bodis-Wollner et al. (1978) found spatial frequency deficits in 17 of 24 M.S. patients; the majority of eyes (16 of 28) had high frequency losses, with most other eyes (10 of 28) demonstrating a flat visuogram (indicating a generalized reduction in sensitivity at all frequencies). Selected reductions in contrast sensitivity to specific spatial frequencies may be affected by the orientation of the grating. Regan and colleagues (1980) demonstrated such orientation-specific losses in 6 of 8 M.S. patients assessed.

Sensitive tests such as the ones described are not specific for M.S. However, they may assist the clinical diagnosis of the disease by objectively demonstrating the presence of lesions in the visual system which may not be detectable with more conventional testing. Different tests may reveal deficits in different patients - VEP delays versus

perceptual delays (Regan, Milner and Heron, 1976); the same test with a different stimulus may be abnormal in different patients - flash versus pattern-reversal transient VEP (Halliday, McDonald and Mushin, 1972); the same stimulus assessed with different tests may be affected differently in different patients - response to a sinusoidal grating pattern measured by VEP and psychophysical methods (Bodis-Wollner et al. 1977). This does not necessarily indicate one test is 'better' or 'best' but rather that complementary information may be obtained by a battery of tests. The composition of that battery will reflect not only potential benefits from information gained, but the constraints of a clinical assessment situation. This study investigates whether the parameter of color vision should be one of the options considered when investigating M.S. patients. To make this question more meaningful, the next section includes some background on color vision.

1.3 COLOR VISION

1.3.1 Normal Color Vision

Two major features characterize the observer with normal color vision: color matching performance (trichromacy) and chromatic discriminative ability (opponency) (Pokorny et al. 1979). It is hypothesized that vision is trichromatic at the receptor level but that opponent processing occurs post-receptorally.

1.3.1.1 Color Matching (Trichromacy)

Current research suggests that humans and other primates have only three types of cones. Trichromatic theory is in accord with these findings since it assumes that any color can be matched (or generated) with a combination of three appropriately chosen primaries. A number of techniques have been employed to determine the spectral sensitivity of the cone photopigments which would represent the three primaries of normal trichromatic vision. These include direct measuring, psychophysical methods and theoretical calculations involving linear transformation of color-matching data.

Direct methods include retinal densitometry, which measures reflected light *in vivo* (Rushton 1972), and microspectrophotometry, which measures light transmitted through cones *in vitro*. By microspectrophotometry the peak sensitivities of the cones were found to be near 420 nm (violet), 535 nm (green) and 565 nm (yellow-green) (Bowmaker and Dartnell 1980). Psychophysical methods involve partial bleaching procedures which measure the response of one cone type while depressing the sensitivity of the remaining cones. The "corneal" sensitivities of the photopigments measured psychophysically are shifted because of selective absorption of short wavelengths by the lens and a pre-receptoral yellow macular filter. With a variation of the Stiles increment threshold technique Wald (1964) determined three overlapping functions with peaks near 430 nm (blue), 540 nm (green) and 575 nm (red). Results vary, depending not only on the method used but also on the

particular technique. However, what is more significant, is the similarities in the values obtained for the spectral sensitivities of the three primaries.

For simplicity I shall refer to the three types of photopic photoreceptors as "blue", "green" and "red"-sensitive cones. However, it must be emphasized that wavelength affects only the probability that a photon will be absorbed by a particular cone. An individual cone does not register color as we eventually perceive it and thus may be considered color-blind. This doctrine was articulated by Rushton in his 'Principle of Univariance' (Mollon 1982).

It is possible to do color matching with a variety of primaries. In 1931 the Commission Internationale de l'Eclairage (CIE) established the colorimetric 'normal observer' based on data from Guild and Wright. The red, green and blue primaries of 700 nm, 546.1 nm and 435.8 nm, normalized to equal intensity white, may be plotted on a chromaticity diagram. The CIE diagram (see Figure 1) is intended only as an objectively defined standard for evaluation and comparison of colors; it is not intended to represent the physiological processing of three real cone primaries in the human visual system.

As with the Maxwell color triangle, a given hue may be expresed as coordinates on the diagram. By definition the sum of the chromaticity coordinates is one, so if two coordinates are specified the third can be readily calculated. Colors are most frequently specified by giving the two chromaticity coordinates of X and Y.

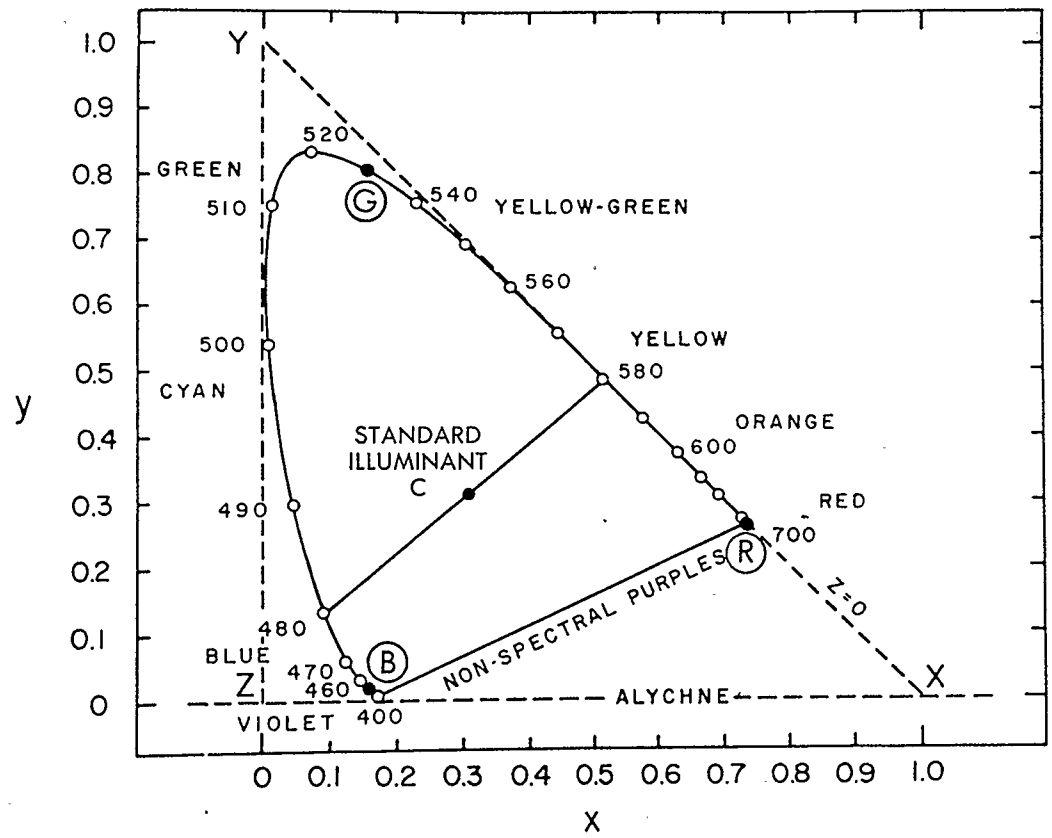


Figure 1 CIE Chromaticity Diagram:
XYZ - imaginary primaries, not experimentally realizable.
RGB - positions of real primaries.

(modified from Pokorny et al. 1979, p. 49 and Lakowski 1969, p. 183)

1.3.1.2 Chromatic Discrimination (opponency)

Although the cone sensitivity maxima are distinctly separate, all three sensitivity curves referred to in the previous section are broadband with considerable overlap, particularly for the red-sensitive and green-sensitive cones. Thus a particular wavelength may stimulate all three classes of cones to a varying degree. The interaction of signals arising from the relative stimulation of the three cone classes is theorized to occur in an opponent manner in some higher-order visual neurons. This is due in part to the observation that judgment of hue differences reflects two independent assessments, of redness versus greenness and of blueness versus yellowness. In addition, under normal viewing conditions, the antagonistic halves of each pair are mutually exclusive, i.e. one does not normally see a reddish-green color. Other perceptual phenomena which suggest opponent-processing include successive contrast effects (including afterimages), simultaneous contrast phenomena, and the observation that chromatic discriminative losses occur independently for red-green or blue-yellow comparisons (Hurvich, 1981, p. 17). Three opponent channels are hypothesized, two chromatic ones (red versus green, blue versus yellow) and one achromatic one (black versus white) (Hurvich, 1981, p. 128-134).

1.3.2 Abnormal Color Vision

Defects in color vision have been classified according to a number of criteria including: the presumed origin of the disorder (congential or acquired); performance on color tests; and the presumed von Kries mechanism of the disturbance.

1.3.2.1 Classification

Classification by Origin

Congenital color vision losses are sometimes referred to as primary, stationary, or hereditary, reflecting their long-standing, stable nature. Acquired defects of color vision are secondary to a pathological disorder and may improve or deteriorate as a function of the underlying condition. Congenital problems are usually the same in both eyes; involve specific, characteristic areas or axes of color discrimination loss; and most commonly involve red-green deficiencies. Acquired problems may affect one or both eyes to a varying degree; involve much less well defined spectral areas of loss which may produce conflicting results on different color vision tests; and frequently involve blue-yellow as well as red-green losses (Linksz 1969; Krill and Fishman 1971; Francois and Verriest 1961). Although both conditions may coexist with unrelated refractive or ocular media defects, visual acuity losses or visual field defects caused by, or linked to, the underlying

condition are much more likely with acquired color vision problems than congenital ones. Object color naming may be quite good in a subject with a congenital color vision disturbance (despite marked losses evident with color vision testing), since he may use other cues such as brightness and learned color names of familiar objects for identification. Conversely, the person with a recently acquired color vision disturbance is much more likely to mis-name color or describe the distorted appearance of an object which he perceived normally in the past.

Classification by Performance on Color Vision Tests

Color matching performance nomenclature is based on the number of primaries an observer requires to match all colors in the spectrum. A trichromat will require three. An anomolous trichromat will also require three, but the relative proportion of the three primaries will differ from that required by a normal trichromat. A dichromat needs only two primaries for a full-spectrum match, and a monochromat only one.

Chromatic discrimination losses may be described qualitatively by a particular axis (either red-green or blue-yellow) or a generalized loss in wavelength discrimination; or quantitatively as mild, moderate or severe.

Classification by von Kries Mechanism

An absorption system is caused by an abnormal pre-receptoral filter and can be mimicked by placing an appropriate filter in front of a normal eye. An alteration system occurs when one (or more) of the visual photopigments differs from that (those) of normal trichromats. It is characterized by non-acceptance of the normal color matches. Specialized pyschophysical testing reveals evidence of a change in the photopigment absorption spectra. A reduction system occurs either by the loss of one of the normal receptor mechanisms or by the collapse or fusion of two normal receptor mechanisms. The reduction system is characterized by acceptance of both normal and abnormal color matches, while chromatic discrimination is severely reduced (Pokorny et al. 1979).

1.3.2.2 Congenital Color Vision Defects

An atheoretical nomenclature derived from Greek was introduced by von Kries in the late 1800's and applied to the hypothesized absent color sensation: protan (first type, applied to "red-blind"), deutan (second type, applied to "green-blind"), tritan (third type, applied to "blue-blind") and tetartan (fourth type). Currently, congenital color vision defects are classified according to a mixture of theories and terminologies. These may include characteristic color confusions which can be displayed on a chromaticity diagram, color matching performance

(tri-, di- or monochromats), von Kries mechanisms (alteration or reduction) and/or hue discrimination ability which may provide an axis of discrimination loss. Figure 2 provides the confusion loci for various color deficiencies. All hues along these lines will appear the same to the affected observer, thus they are termed isochromatic lines. The broad axis of confusion is red-green for both protan and deutan and blue-yellow for tritan and tetartan. The specific color confusions are evident by examining the neutral axis for each condition, for example a protanope will confuse blue-green with red but can differentiate yellow from blue.

Most congenital color vision defects involve absent or weak red-green discrimination. It may be the less severe "alteration" form (protanomaly or deuteranomaly) in which color vision is still trichromatic but one of the photopigments differs from normal. Or, it may be the more severe 'reduction' form of protanopia or deutanopia. There seems to be general acceptance that protanopia is due to a 'red' (receptoral) defect, with loss of long wavelength luminosity sensitivity. Since visual acuity is normal it is possible that the red photoreceptor is still present but contains chlorolabe, the green-sensitive photopigment rather than erythrolabe, the red-sensitive pigment (Boynton 1979, p. 342). There is some controversy in the literature over the basis of deuteranopia. Early color vision theorists (Fick and Leber 1870; see Boynton 1979, p. 358) proposed that deuteranopes have normal red and green photoreceptors and pigments, but a fusion of neural pathways from the cones results in a post-receptoral mixing of those

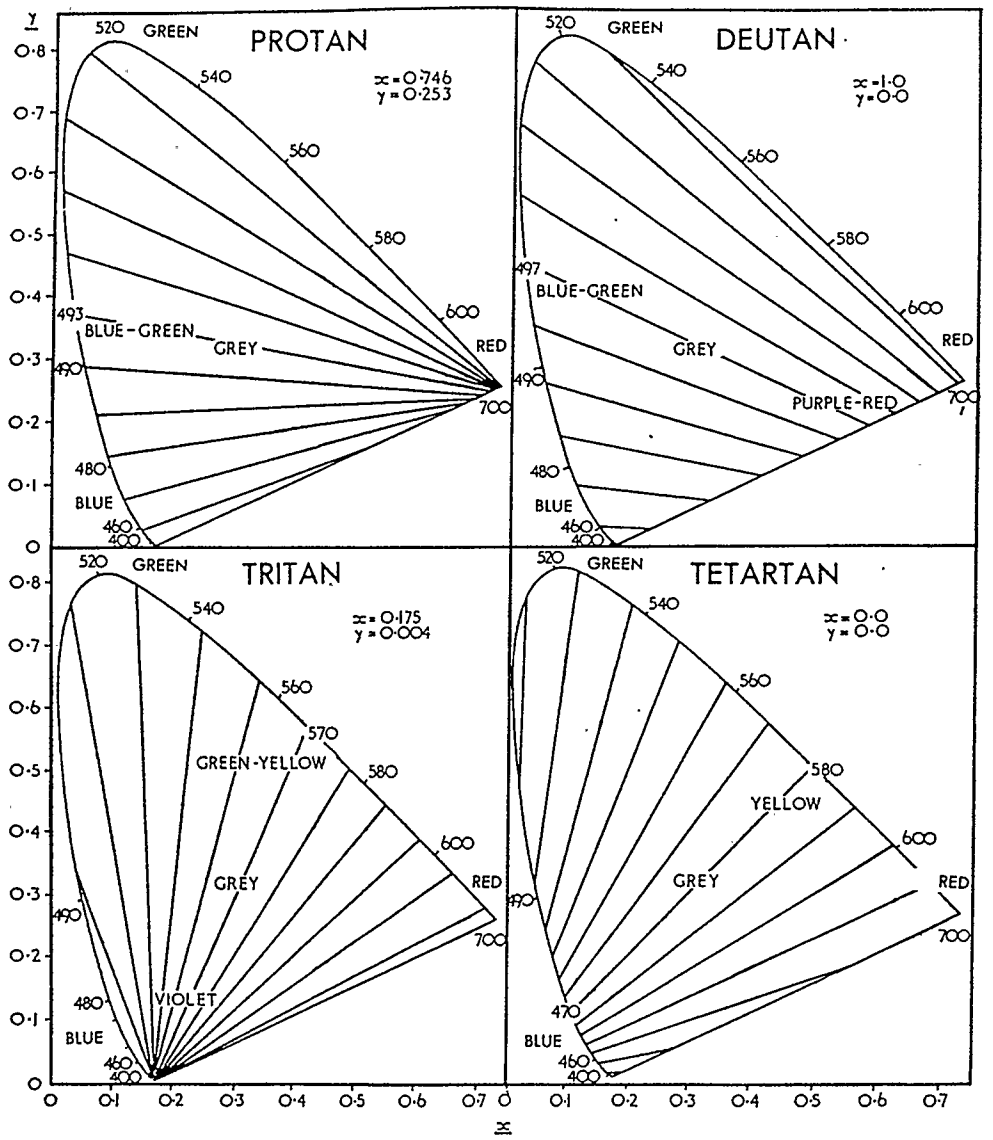


Figure 2 Isochromatic Lines in Four Types of Dichromatic Conditions. (modified from Lakowski 1969, p. 187)

primaries. Current authors (Alpern, Mindel and Torii 1968) postulate that deuteranopia is analogous to protanopia, i.e. red-sensitive erythrolabe has replaced green-sensitive chlorolabe in what should be green-sensitive cones. On some tests some deuteranopes show a slight loss in relative luminosity efficiency at short wavelengths (Pokorny and Smith 1979, p. 207). However the luminosity curves of most deuteranopes are difficult to differentiate from those of normal subjects (Boynton 1979, p. 358). Is this because some deuteranopes do indeed have normal red and green receptors whose pathways are fused post-receptorally? Or could it be that the red cones make such a dominant contribution to normal luminosity (Vos and Walraven 1970) that much less of a luminance sensitivity loss occurs than one would normally expect in the absence of chlorolabe (Boynton 1979, p. 359)? Wald's view (1966) is similar: "though the green-receptor, which accounts principally for protan luminosity curve, fails badly in the red, the red-receptor, which mainly accounts for the deutan luminosity curve, does not fail correspondingly in the green".

Congenital blue-yellow defects, both the classically recognized alteration form of tritanomaly (abnormal blue pigment) and the more severe reduction form of tritanopia (blue receptor or pigment absent), are much rarer. Muller in 1924 and Judd in 1943 (Pokorny et al. 1979, p. 77) postulated two reduction forms of blue-yellow defects to correspond to the early theories of red-green defects: tritanopia indicating a receptoral defect and tetartanopia a post-receptoral defect. To date there has not been a documented case of a congenital

tetartan defect. However, observers with an acquired color defect may demonstrate a discrimination loss along the tetartan axis (see Figure 2).

1.3.2.3 Acquired Color Vision Defects

Some of the classifications applied to congenital color vision anomalies are also used in describing acquired defects. However, the same term may have a somewhat different meaning. In the context of the acquired color vision disturbance the color-matching performance terms of trichromatic, dichromatic and monochromatic may be quantitative, reflecting, to a certain extent, the severity of the defect. They do not imply specific malfunction or non-function of one of the three cone receptor mechanisms as is the case in congenital disturbances.

Classification according to the major axes of discrimination loss as proposed by Verriest (1963) seems to be a fairly widely accepted method. Verriest described four types of acquired color vision deficiencies: a nonspecific loss with no prominent axis; red-green Type I losses (with changes in the photopic luminosity curve); red-green Type II losses (with approximately normal photopic luminosity curve); and blue-yellow losses.

When establishing norms to differentiate pathologically abnormal color vision from variations within a normal population, one must consider possible aberrations inherent in the test. Another consideration is the effect of aging, which may cause loss of short (blue) wavelength

sensitivity primarily because of senile discoloration of the lens (Lakowski 1962).

Cortical disturbances may cause some unusual types of color vision abnormalities. These include coloropsia or chromatopsia (a "perversion" of color vision in which white stimuli appear colored), color agnosia (an inability to recognize and appreciate colors), and disturbance of color naming. Despite normal colorimetric performance and chromatic discrimination, the affected observer may be unable to name colors correctly or to associate color names with their usual meanings (Birch, in Pokorny and Smith 1979).

1.4 Color Vision and Visually Evoked Potentials

The VEP is an increasingly widely used clinical tool to objectively document visual system involvement in M.S. patients, both with and without other indications of visual abnormalities (Halliday, MacDonald and Mushin 1977). In our VEP investigations the stimulus used was a small (27.5' arc), black and white, high contrast, sharply focused, checkerboard pattern with a slow reversal rate (1.88 Hz). The VEP was recorded with a scalp electrode over the occipital cortex. With this arrangement it seemed reasonable to assume that the waveform we recorded reflected primarily the function of the foveal region (Harter 1970; Riggs and Wooten 1972). Since the fovea is also critically important for color vision we were interested in evaluating the relationship between color vision performance and VEP response. In

some circumstances changes revealed by the VEP and psychophysical testing are correlated; Harter and White (1968) demonstrated two components of the VEP which varied in amplitude in close agreement with the subjectively observed clarity of a stimulus pattern. In other cases there is no agreement between the two methods; Bodis-Wollner et al. (1979) found no correlation between an abnormal VEP latency to a grating stimulus and an abnormal psychophysically determined 'visuogram' (see Section 1.2.4) in a group of 13 M.S. patients. The three studies which are included in the following discussion are particularly relevant to the question of the relationship between color vision and pattern reversal VEP.

Wildberger and van Lith (1976) compared pattern-reversal VEP with performance on the Farnsworth Panel D-15 and the Farnsworth-Munsell 100-Hue test in patients with optic neuritis. In the acute phase the VEP and color vision were both abnormal in all 12 affected eyes. The defect was red-green in 6/12 eyes, blue-yellow in 2/12 eyes and unclassifiable in 4/12 eyes. In the early recovery period (up to 3 months after onset) in the same group of patients the VEP remained abnormal but color vision returned to normal in 4/12 eyes with the Panel D-15. In the late recovery period (4-24 months after onset) in another group of 16 patients, the VEP was normal in only 1/20 eyes but color vision was normal in 14/20 eyes with the FM 100-Hue test and 17/20 eyes with the Panel D-15.

Griffin and Wray (1978) compared pattern-reversal VEP with performance on the FM 100-Hue test and the Ishihara pseudoisochromatic

plates in 23 patients with idiopathic retrobulbar neuritis (RBN) with acuities recovered to 20/40 or better. There were 30 eyes with RBN; 16 unilaterial cases and 7 bilateral cases. Color vision with the FM 100-Hue test was abnormal in all of the affected eyes as well as 10 eyes judged clinically normal. The VEP was abnormal in 28/30 affected eyes and 1 of the clinically normal eyes. The Ishihara test was less useful; it revealed deficits in 14 unilateral cases and 1 bilateral case. Unlike Wildberger and van Lith, these authors found the FM 100-Hue test to be superior to the VEP in detecting disturbance of visual function.

Finally, Rigolet and colleagues (1979) compared VEP and color vision with the AO-HRR plates and the FM 100-Hue test in patients diagnosed as possible, probable or confirmed M.S. by the criteria of McAlpine et al. (1965). They found VEP delays in all eyes with a previous history of retrobulbar neuritis (RBN) i.e., 34 eyes in 27 patients. There were also abnormal latencies in one or both eyes of 68 percent of 75 patients with no previous evidence of RBN. The highest percentage of these previously undetected abnormalities occurred in patients diagnosed as "definite" or "probable". Rigolet et al. (1979) found that color vision was normal in 98/162 eyes (84 patients). In patients with color vision disturbances the axis was red-green in 48/162 eyes; six of these 48 were considered to be congenital color vision defects. All of the eyes showing acquired red-green deficits also showed an abnormal VEP latency. There was a yellow-blue deficit in 10/162 eyes, half of which had VEP abnormalities, and a nonspecific

deficit in 6/162 eyes, five of which had abnormal VEP. In total, abnormalities were present with color vision testing in 64/162 eyes, compared with VEP abnormalities in 104/162 eyes. The authors considered color vision testing an excellent screening test for anterior visual system pathology, but if this was normal they felt a VEP examination would be indicated. They suggested that only limited cases would require both the VEP and color vision testing to confirm the diagnosis of visual system involvement.

These reports are ambiguous as to which is the more sensitive test. It is unclear what the relationship is between color vision losses and VEP abnormalities. In addition these studies have focused on color vision and VEP testing only as they relate to retrobulbar neuritis. This study investigates the relationship between VEP abnormality and color vision losses. The question of retrobulbar neuritis is considered as a separate issue since it is clear from autopsy studies that visual system lesions in M.S. can be present in sites other than the optic nerve (Lumsden 1970).

II. MATERIALS AND METHODS

2.1 COLOR VISION TESTS

Color vision tests vary in their purpose, design and format. Therefore subjects will not necessarily perform equally well (or poorly) on all tests. This discrepancy in results between various tests may be particularly evident in patients with acquired dyschromatopsia. It has become common practice to utilize a battery of color vision tests in the investigation of color vision problems. In the following section the color vision tests which were utilized for this study are discussed under three general headings: confusion tests, hue discrimination tests and colorimetric tests.

2.1.1 Confusion Tests (Pseudoisochromatic test plates)

Pseudoisochromatic tests utilize individual test plates composed of surface colors in a dot format, featuring multicolored numbers or figures against a multicolored or neutral background. The hues for the figures and background lie on the axis of confusion for known color deficiencies, most commonly on the protan or deutan axis. Thus the plate will appear uniform or 'isochromatic' to a color defective observer. The effectiveness of the plate depends on the colors used, the luminance contrast between the symbol and the background, and the parameters of the dot format (Birch-Cox 1976). Many of the plates were

constructed by trial and error before accurate colorimetric measurements were possible, to differentiate subjects with congenital color vision deficiencies from normal trichromats. Some of the plates are not ideally designed, since the chromatic differences between figure and surround do not lie precisely on the isochromatic confusion lines. In some cases, however, this discrepancy allows additional information to be extracted about color discrimination.

The Ishihara is the most commonly used pseudoisochromatic test. It is generally regarded as the best test of this type to screen for congenital protan or deutan observers. However it has no provision for assessing "blue" deficits (either tritan or tetartan) and thus has limited use in the assessment of acquired color vision problems. Another popular test in this format is the American Optical-Hardy, Rand and Rittler series of plates (AO-HRR). Although this test is not as good as the Ishihara for distinguishing red-green defects, it provides screening and diagnostic plates for tritan defects. Both the Ishihara and AO-HRR plates were used in this study to provide the maximum information that can be expected from this format. Pseudoisochromatic test plates are useful for quickly identifying subjects with severe color vision disturbances, and to screen for congenital dichromats. However, they are not suitable for quantifying the severity of the defect by using the number of plates missed as a criterion (Lakowski 1966).

2.1.2 Hue Discrimination Tests

The Farnsworth-Munsell 100-Hue Test (FM 100-Hue) provides a sensitive full-spectrum assessment of hue discrimination. Compared to more elaborate psychophysical tests it is relatively inexpensive ($300-400) and fast (approximately 1/2 hour for completion and 1/4 to 1/2 hour for error score calculations). There is a large body of literature available on this test, including standards for its use, and descriptions of its reliability in assessing known color deficiencies. It provides a qualitative and quantitative assessment of color deficits and is therefore useful in monitoring changes in an acquired color vision abnormality.

The FM 100-Hue test consists of a series of circular Munsell-colored papers mounted in black caps. All caps are of equal saturation and brightness (Munsell Chroma 6 and Value 6). Thus hue discrimination for surface color is the only variable being tested. Eighty-five movable caps are distributed in four boxes. Each box has 21 movable caps (22 in box #1) with fixed reference caps at the beginning and end of each box. The subject is asked to form a continuous series of colors between the two fixed reference caps. After each box is arranged by the subject, the examiner scores the arrangement according to the numbers on the back of each cap. The calculated error score is then plotted on a circular score sheet.

Areas with increased error scores (representing spectral regions of decreased discrimination) appear on the circular diagram as a

bipolar axis or a monopolar bulge. The Dichotomous Test for Color Blindness (Panel D-15) is another hue-discrimination test which is similar to the FM 100-Hue test, but simpler in format. There are 15 movable caps and one fixed reference cap, similar in chroma to the FM 100-Hue test. The caps are chosen to lie on the isochromatic lines of known deficiencies. Therefore, in addition to calculating an error score, one may also determine an axis of confusion. The test is useful for a rapid determination of a moderate or severe chromatic discrimination loss but is not as sensitive as the FM 100-Hue test.

2.1.3 Colorimetric Tests

Another method of assessing normal and defective color vision is colorimetry. This is the discipline of color measurement and specification based on the concept of equivalent-appearing stimuli (Pokorny and Smith 1979, pp. 23 and 38).

An observer with normal trichromatic color vision can match all hues by appropriate adjustment of three primary lights. Typically a test color and one primary are matched to a mixture of the two remaining primaries. However, this type of full spectrum matching is very tedious and time-consuming. Therefore special color matches (termed equations) have been developed that make use of only two primaries which are matched to a standard test light. The resulting matches appear to be the same in hue and brightness and are termed metamers. Simplified colorimeters which utilize these equations are

called anomaloscopes.

In our study the Pickford-Nicolson (P-N) anomaloscope was used. Since it has three equations: red-green, blue-yellow and green-blue, it is particularly appropriate for assessing acquired disturbances of color vision which frequently affect the "blue" system. Although the Nagel anomaloscope is more commonly used, in its commercially available form it tests only the red-green equation with no provision for assessing tritan or tetartan defects. The P-N anomaloscope is mechanically and optically simple. There is no lens system. The essential colorimetric components include: a set of glass color filters, a light source, a sanded glass panel over the viewing aperture and coated integrating chambers (Pickford and Lakowski 1960). Testing is usually performed with the subject sitting one meter in front of the instrument. The variable circular aperture is adjusted to subtend a visual angle of 1 1/2 degrees, thus assessing primarily foveal vision. The retinal illumination is about 80 trolands which is within the photopic range of adaptation. Since there is some ambient illumination and the subject is not staring into a telescopic aperture, it is not necessary to adapt the subject to photopic levels with a Trendelenburg screen as is the case with the Nagel anomaloscope. In Figure 3 these equations are plotted on the CIE color space diagram with the isochromatic lines for the established types of dichromatism (Lakowski 1971, p. 168). The instrument allows the investigator to vary not only the relative proportions of the two primaries, but also the luminance of the test light and adjust it for each primary mix.

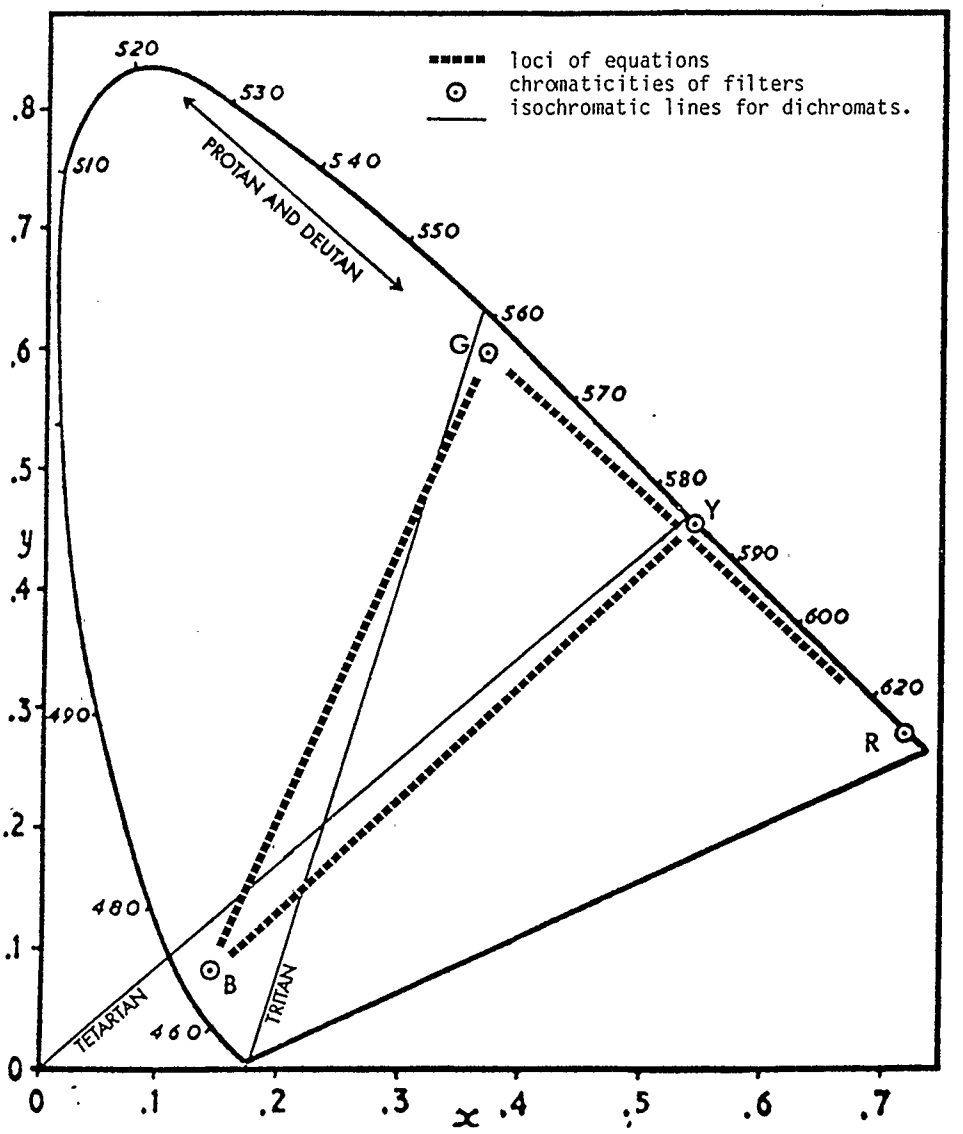


Figure 3 Pickford-Nicolson Anomaloscope, demonstrating loci of equations, chromaticies of filters, and isochromatic lines for dichromats, on CIE diagram.

(modified from Lakowski 1971, p. 168)

Two measurements may be made on an anomaloscope, the matching range and the mid-matching-point setting. It was the matching range which was of greatest interest in this study. The matching range is a measure of wavelength discrimination. It allows assessment of the 'interval of equality' or range over which a combination of the two test primaries (for example red and green) is perceived as corresponding to the test light (in this example yellow). This is particularly useful for evaluating patients with acquired color vision anomalies. Mean matching ranges may be calculated and compared for different groups (e.g. patients and controls). If the results are recorded in 'just noticeable difference' units, then results may be more easily compared between various instruments and studies.

2.2 CONVENTIONAL CLINICAL TESTING

2.2.1 Subjects

Forty patients with M.S. were investigated. Patient selection was based on the results of visually evoked potentials (VEP) recorded at the Calgary General Hospital. Three groups of patients were identified from their past VEP records. When the VEP was repeated for this study, differences were evident for some patients between the initial and repeated VEP latencies. This altered the number of patients in the various groups somewhat.

Group 1: VEP normal in one eye, delayed P1 in the other eye (on one or both assessments) normal P1 = up to 116 msec.

From records, n = 20 patients (40 eyes)

Following repeat VEP, n = 14 patients (28 eyes)

Group 2: VEP delayed P1 latencies in both eyes

From records n = 10 patients (20 eyes)

Following repeat VEP:

Group 2A - slightly delayed latencies both eyes (P1 = 118-128 msec.):

n = 4 patients (8 eyes)

Group 2B - extremely prolonged latencies both eyes (P1 > 130 msec.):

n = 15 patients (30 eyes)

Group 3: VEP normal in both eyes.

From records, n = 10 patients (20 eyes)

Following repeat VEP, n = 7 patients (14 eyes)

A group of 27 control subjects (54 eyes) matched to the patient group by age and sex was also evaluated.

2.2.2 Evaluation Procedure

For this study all patients were evaluated with the following tests: visual acuity - at 1/3 meter and six meters; visually evoked potentials following monocular then binocular stimulation; a

neurological assessment including fundus examination and static visual fields on the Friedman analyzer; a binocular vision investigation; and a color vision evaluation. All of the above tests were completed on the same day. There was a time lapse between the the date of the VEP which was used for the original patient selection and that of the VEP which was repeated during this study. The time interval between the dates of these two VEPs varied from 4 months to 36 months with a mean of 18 months.

A history of optic neuritis was assumed if either: (a) there was a history of visual signs or symptoms including reduced visual acuity or visual field deficits, or (b) there was optic atrophy (as evidenced by pathologically pale optic discs) at the time of this examination.

Following the neurological examination patients were classified by the criteria of McDonald and Halliday (1977) (see Appendix Table A1) and their disability evaluated on a scale from K0 to K10 suggested by Kurtzke (1965). Although patients were not diagnosed on the basis of the cerebrospinal fluid findings (i.e. increased proportion of IgG or oligoclonal bands) or the evoked potential findings, these results confirmed the clinical diagnosis and would have resulted in a more "definite" classification in a number of patients.

2.2.3 Visually Evoked Potentials (VEP)

Visually evoked potentials were elicited with a CRT stimulator, recorded and displayed with a Nicolet CA 1000 signal averager. The stimulus was a high-contrast 27.5 minute check pattern reversing at 1.88 Hz. Potentials were recorded from Oz to Cz electrodes with the ear as ground. The VEP was considered abnormal if: (a) the latency of the first major positive peak (P100 or P1) exceeded 116 milliseconds (msec), or (b) if the interocular difference was greater than 6 msec (both criteria exceeded our normal mean by three standard deviations).

2.2.4 Color Vision Testing

Color vision was assessed with the City University Plates, the American Optical-Hardy Rand Rittler Plates (AO-HRR), the Ishihara Plates (the first 25 plates of the 38-plate series in the 1981 edition), the Farnsworth Dichotomous Test (Panel D-15), and the Farnsworth-Munsell 100-Hue Test (FM 100-Hue) (see appendix for acquisition survey). Illumination for color vision testing was one Verilux Daylight Bulb with a correlated color temperature of 6,200°K and a color-rendering index of 93, giving an illuminance of 645 Lux. We had the capacity to decrease the illuminance to 375 Lux by substituting a MacBeth Daylight Lamp or to increase it to 1,665 Lux with two Verilux Bulbs plus the MacBeth Lamp. Testing was done against a neutral grey flannel backdrop and table cover; test plates were positioned on the

MacBeth Daylight Lamp stand to maintain a constant angle to the light source and the subject; the testing distance was one meter. All tests were used, unaltered, as received from the manufacturer, and except for the Farnsworth-Munsell tests were administered according to the instructions provided by the manufacturer.

The Farnsworth-Munsell tests were administered according to the manufacturer's instructions, with two exceptions: (a) time allowed for each box was not restricted; and (b) the colored caps with the Panel D-15 and FM 100-Hue were displayed for subject selection in random order on the neutral grey table cover to facilitate handling, since some of our patients had difficulty with fine motor control. In cases of severe disability the patient would point to the cap he wished to select and the examiner would place it in the wooden case.

The FM 100-Hue error scores were calculated two ways: 1) manually and 2) using a computer programme modified by Mr. David Orford from a programme kindly provided by Dr. John Parker. Dr. Parker's programme reflects his rearrangement of the contents of the four boxes of the FM 100-Hue (Parker 1979). Our programme allowed analysis of information from an unaltered FM 100-Hue test set.

Two alternative methods have been described for plotting FM 100-Hue error scores on the circular graph which accompanies the score sheet (Farnsworth 1957; Kinnear 1970). The error score calculation is the same in both methods. For each numbered cap the difference in number between the cap and the caps on either side is determined; the differences are added and the sum is adjusted by subtracting two (i.e.

the sum of differences obtained for arrangement in proper sequence). In the Farnsworth mode of graph plotting the individual error score is plotted for each cap number; whereas in the Kinnear mode the individual error score is plotted for each position number. Kinnear suggests that while the resulting graphs are similar, his method is easier to plot and tends to group errors together, making the axis somewhat more obvious.

2.3 ANOMALOSCOPE TESTING

2.3.1 M.S. Patients

The Pickford-Nicolson (P-N) anomaloscope was used to assess color vision in each eye of 10 M.S. patients. Nine patients had a past history of optic neuritis (either visual signs, symptoms or optic atrophy) in one eye, but were not in an acute phase at the time of testing. The other eye in these patients was clinically normal with visual acuities of 20/20 in seven patients and 20/30 in two patients. The remaining patient (C.B.) previously had experienced bilateral attacks of optic neuritis. On the day of her anomaloscope examination she had acute optic neuritis on the right side. Her findings are considered separately and were not used for calculating mean data.

Nine patients had been assessed as part of the investigation described in Section 2.2. The time lapse between the previous investigation and this anomaloscope study varied from two to five months (mean

3.4 months).

The FM 100-Hue test was administered again to most patients in this study on the same day as the anomaloscope examination. The FM 100-Hue test was not repeated in two patients who had achieved a normal score on the 100-Hue test previously (mean score for the four eyes was 64) and whose anomaloscope findings were normal, or by the patient who was in the acute phase of optic neuritis, because of her visual discomfort.

2.3.2 Comparisons

For a comparison of color vision losses revealed by anomaloscope testing in M.S. patients and in patients with raised intraocular pressure, charts were selected at random from the files of the Ophthalmology clinic at the University of British Columbia for patients with glaucoma (N=11 eyes) and ocular hypertension (N=7 eyes). An attempt was made to match patients by age. However glaucoma and ocular hypertension generally tend to affect an older population than does M.S. Therefore the mean ages of the patients with raised intraocular pressure (glaucoma mean age = 36.1 years, ocular hypertension mean age = 43.1 years) are higher than the mean age of the total M.S. patient group (mean age = 32.6 years).

Direct comparisons were made between M.S. patients age 36 to 45 years (mean age = 39.7 years, n = 6 eyes) and ocular hypertensive patients (mean age = 43.1 years, n = 7 eyes). Only these two groups

were compared for the following reasons:

1) These groups were more closely matched in age than were the 'total' group of M.S. patients and the patients with ocular hypertension. This is an important consideration since increasing age is known to significantly diminish color vision performance (Lakowski 1971);

2) All glaucoma patients were on miotic therapy which reduced pupil size to about half normal diameter (approximately 2 mm compared with a normal diameter of 4.5 mm). One might expect that this reduced pupil size would impair performance on color vision testing by a factor of more than two on the FM 100-Hue test and the two 'blue' anomaloscope equations; and by a factor of more than more than four on the red-green anomaloscope equation (Lakowski and Oliver 1974). Thus it may be anticipated that the performance of glaucoma patients on the anomaloscope exaggerated the degree of neurological impairment.

III. RESULTS

3.1 CONVENTIONAL CLINICAL TEST RESULTS

3.1.1 Screening Tests

City University Test

In the patient group, errors were made in only 2 of 80 eyes tested (2.5%): Plate Number 3 was missed by one patient viewing with the right eye, Plate Numbers 5 and 8 were missed by another patient viewing with the right eye. In the control group, no errors were made viewing with either eye.

Panel D-15 Test

In the patient group errors were made viewing with 12 of 80 eyes (15%). There did not appear to be any pattern to the caps which were missed. In the control group, errors were made viewing with 6 of 54 eyes (11.1%); as in the patient groups no significant pattern was evident in the occurrence of errors.

AO-HRR Plates

In the patient group, errors were made viewing with 26 of 80

eyes (32.5%) in 20 of 40 patients. Plate Number 3 was missed by all those who made errors and was the only misjudged plate in approximately half of the sample in which the errors occurred (i.e. 12/26 eyes). In the control group Plate Number 3 was missed by only one subject using either eye, giving an error frequency of 2 of 54 eyes or 3.7%.

Ishihara Plates

It was difficult to distinguish between patients and controls on this test. Both groups had excessive difficulty with plate number 7 (the 3 was reported as 8), number 9 (the 74 was reported as 71), number 12 (the 97 was reported as 87), number 17 (the 73 was reported as 78 or 23), and numbers 18 to 21. While plates 18 to 21 are intended to be seen as non-representational patterns, a high proportion of both patients and controls reported numbers present, particularly in plate number 20 in which the number 45 was identified (see Table 1 for details). There were not many patients or controls who had difficulty with the diagnostic plate numbers 22 to 25; most errors on these plates were made by patients with extremely prolonged VEPs in both eyes.

There was a higher proportion of subjects who made no errors on any plates in the control group (30%) than in the patient group (12.5%). Among subjects who did make errors, however, the "number of errors per eye" was similar for the control group (3.1) and the patient group (3.5).

The most satisfactory Pass/Fail criterion for the Ishihara

TABLE 1 ISHIHARA PLATES: Errors Made on Each Plate and the Most Common Mistake for Each Plate by Patients and Controls

Plate Number	Errors				Correct Response	Most Common Error	
	Controls/54		Patients/80			Controls	Patients
1	D E M O N S T R A T I O N		P L A T E		12		
2	-	-	-	-	8	-	-
3	-	-	-	-	6	-	-
4	2	(3.7%)	5	(6.3%)	29	20	20
5	-	-	4	(5.0%)	57	-	67
6	-	-	-	-	5	-	-
7	11	(20.4%)	13	(16.3%)	3	8	8
8	-	-	2	(2.5%)	15	-	*
9	8	(14.8%)	18	(22.5%)	74	71	71
10	1	(1.9%)	1	(1.3%)	2	8	8
11	-	-	5	(6.3%)	6	-	8
12	12	(22.2%)	38	(47.5%)	97	87	87
13	5	(9.3%)	6	(7.5%)	45	46	*
14	-	-	-	-	5	-	-
15	-	-	-	-	7	-	-
16	-	-	-	-	16	-	-
17	15	(27.8%)	30	(37.5%)	73	78;23	78;23
18	8	(14.8%)	18	(22.5%)	No	*	5
19	13	(24.1%)	18	(22.5%)	Number	2	2;8
20	26	(48.1%)	45	(56/3%)	Pattern	45	45
21	15	(27.8%)	20	(25.0%)	Only	*	*
	PROTAN DEUTAN "DIAGNOSTIC PLATES						
22	1	(1.9%)	5	(6.3%)	26	28	28
23	-	-	5	(6.3%)	42	-	4
24	-	-	4	(5.0%)	35	-	3
25	1	(1.9%)	3	(3.8%)	96	86	9

* No consistent error.
- No error made.

plates to differentiate the performance of patients from controls with this test appears to be allowing one error in the first 16 plates, that is, two or more errors are considered a failure. By this standard approximately 30 percent of M.S. eyes (45% of patients) were abnormal and approximately 10 percent of control eyes (or people) were abnormal (see Appendix Table A.2 for details).

3.1.2 Farnsworth-Munsell 100-Hue Test

3.1.2.1 Standards

i) Background: For a careful analysis of FM 100-Hue scores, one must consider: (a) the suggestion that the test is more difficult in the red and blue-green regions (Verriest 1963; Lakowski 1969), and (b) indications that there is a decrease in hue discrimination with age, with the blue-yellow axis much more affected than the red-green axis (Pokorny et al. 1979). This senile diminishing of color discrimination has been partly attributed to changes in the crystalline lens. The increase in optical density of the lens with age is thought to cause a selective increase of absorption at the shorter wavelengths. This hypothesis is substantiated by experiments with young subjects, using a series of progressively more dense yellow filters (Lakowski, 1962; Verriest, 1963). Therefore it is misleading to conclude that anyone with a total error score of 100 has "low discrimination", as suggested by the FM 100-Hue Test Manual (Farnsworth, 1957). In this

study Verriest's (1963) norms were used. He considered an error score abnormal only when it exceeded "that observed in about 95% of an unselected population of the same age group". The norms were determined by testing a total sample of 480 subjects.

ii) Controls: Our control population was used to validate our specific testing situation and to confirm the suitability of using Verriest's norms for this study. The numbers in each age category of our control group were fairly small. Therefore it was not meaningful to use the maximum error score of 95 percent of each age group as the norm for assessing our patients. However it was useful to compare the means and standard deviations for our age-grouped control data with figures published by Verriest (1963) (see Appendix A.3 and A.4).

If two standard deviations above the mean control group error score are used as the criterion for "failure of test" (i.e. any score above this number would constitute an "abnormal error score"), in the majority of age categories this method results in a lower value for the normal limit in our population than in Verriest's; in many cases our criterion, even at 3 S.D. above the mean, is lower than Verriest's at 95 percent or 2 S.D.'s (see Appendix Table A.4). The exceptions to this trend in our control data are the two categories which include controls that failed the test by the Verriest "observed" criteria. If these two subjects are excluded, the resulting means and standard deviations produce pass/fail criteria which are much more in line with the 95 percent observed criteria. The lower "normal" value of our

control population would result in more patient "failures" of the test by our criteria than by Verriest's. By using Verriest's "observed values" criteria rather than our own control data, a conservative approach for assessing patient failure has been adopted. Thus judgments of "abnormality" or "deficiency" appear to be well founded. An additional advantage is that the Verriest standard is widely used which facilitates comparison of results from different places or studies.

In Verriest's data (1963) there is a discrepancy between the error score "observed in about 95 percent of an unselected population of the same age group" and the equivalent score calculated as two standard deviations above the mean (see Appendix Table A.4). The "observed" rather than the "calculated" values were used as pass/fail criterion in the present studies, because they produce a monotonically increasing function with age.

iii) Interocular Differences: Another aspect of the FM 100-Hue test scores investigated was the difference between error scores in the right and left eyes of the same subject which were 'normal' according to the age-related Verriest standard.

The maximum interocular difference in error scores observed in 95 percent of our control population was 45, the interocular difference two standard deviations above the mean was 41, and three standard deviations above the mean was 55. The maximum difference between the square root of the error scores to be considered normal by Aspinall (1974) was

three. The results of these methods in differentiating patients from controls is provided in Appendix Table A.5. The 95 percent criterion (D=45) results in more frequent detection of abnormalities than the more stringent 3 S.D. (D=55) criterion, and a better discrimination of patients from controls than the 2 S.D. (D=41) criterion. Therefore I assumed that a difference in total error score between eyes of more than 45 constituted an abnormal interocular difference.

It is interesting to note that in the control group the eye with the higher score was consistently the right eye, which was tested first, perhaps suggesting that test performance improves with experience or learning. However, in the patient group the higher score was consistently the left eye, tested last, perhaps suggesting that "fatigue" reduces test performance in M.S. subjects.

3.1.2.2 Quantitative Assessment of Abnormalities

i) Percentages: Abnormal performance on the FM 100-Hue test was approximately five times more frequent in the M.S. patient group than in our control group. Using Verriest's "observed" pass/fail criterion for this test, 28/80 eyes (35%) in 17/40 patients (42.5%) were abnormal. By the same criterion 4/54 eyes in 2/27 control subjects (7%) had abnormal error scores. Assuming that an interocular difference in error scores of greater than 45 is abnormal, then three additional patients and one additional control also failed the FM 100-Hue test. This brings the total percentage of abnormalities to 50

percent in the M.S. patient group and 11.5 percent in the control group.

ii) Means (see Table 2): The mean total scores in six of seven age categories are considerably higher for M.S. patients, frequently two or even three times higher, than for Verriest's or our control subjects. In only one age group (45-49 years, with only two patients) the mean was approximately the same for the patient group as for Verriest's group, but still one and a half times greater than for the control group.

To investigate whether the higher means in the patient groups were caused by generally higher scores (or just by the larger number of patients with abnormal error scores), the patient group was further divided into those with "normal" scores and those with "abnormal" scores. Means were calculated for both groups. As expected the means for patients with abnormal error scores were considerably higher than the control means (2-3 times higher on average). However, the means for the M.S. patients with normal total error scores were quite similar to the means for both Verriest's and our control groups. The notable exception was in the 20 to 24 age category, in which the "abnormal" mean was 5.8 times higher than our control group and the "normal" mean was 1.5 times greater than in Verriest's normal group. Usually however, the higher mean scores in the various age groups were not caused by a generalized tendency for M.S. patients to have higher FM 100-Hue scores than the normal population. Rather, these high mean

Table 2 Farnsworth-Munsell 100-Hue Test: Mean Scores for Norms, Controls and M.S. Patients

Age Category	Mean Total Error Scores: Norms (Verriest)	M.S. Patients with Normal Scores (N Eyes)	M.S. Patients with Abnormal Scores (N Eyes)	All M.S. Patients (N Eyes)
20-24	36.3	56.0 (7)	210.0 (3)	114.0 (10)
25-29	47.4	50.5 (9)	139.1 (9)	94.8 (18)
30-34	54.7	47.0 (13)	127.7 (5)	70.9 (18)
35-39	56.8	58.9 (10)	161.3 (8)	104.4 (18)
40-44	62.4	89.8 (4)	181.0 (2)	120.2 (6)
45-49	90.4	89.5 (4)	- (0)	89.5 (4)
50-54	71.5	66.6 (5)	163.0 (1)	82.7 (6)
TOTAL N (Eyes)		(52)	(28)	(80)

Mean scores for M.S. patients with 'normal' FM 100-Hue total error scores were similar to mean scores for Verriest's norms. (Mean scores for M.S. patients with abnormal total error scores, and mean scores for all M.S. patients in each category are much higher than those of norms.)

scores are due to a greater percentage of patients who failed the test.

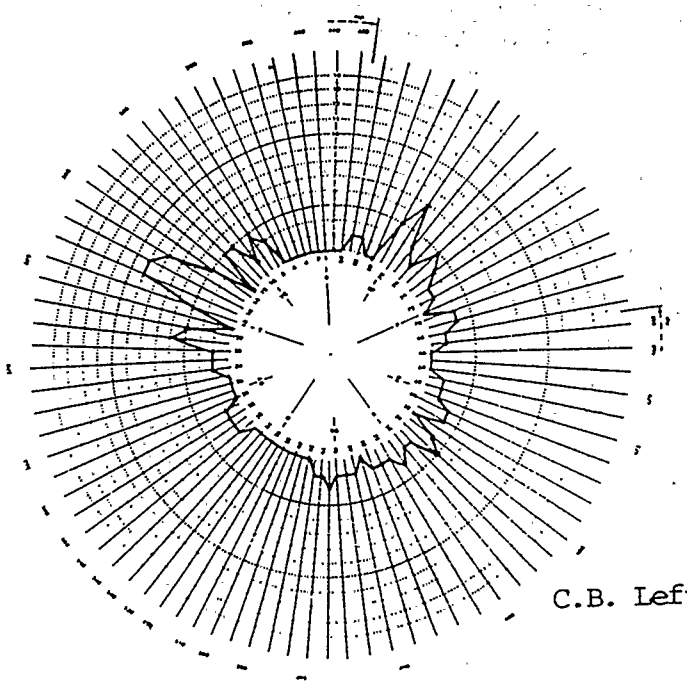
3.1.2.3 Spectral Location of Abnormalities

i) Circular Graphs: A circular graph of error scores may be constructed on the score sheet diagram to determine in which area of the spectrum errors occur. In the Farnsworth mode (1957) the scores are plotted for each movable cap; in the Kinnear mode (1970) the scores are plotted as they occur on the score sheet relative to the correct position of the cap (please refer to Methods, Section 2.2.4, for details).

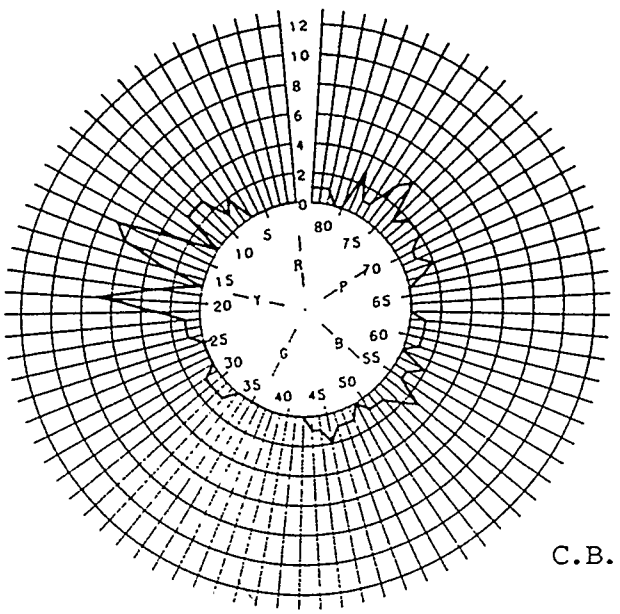
Seven patients (14 eyes) were evaluated by both methods. Error scores were abnormal in 10 eyes, low normal in two eyes, and high but within normal limits in two eyes. Two subjects (4 eyes) with congenital color deficiencies were also evaluated. The Kinnear mode diagrams were drawn manually. The Farnsworth mode diagrams were produced by computer (program for Honeywell/Multics written by Mr. David Orford).

In all cases examined the general axes of the errors were the same by both methods. There were however minor shifts in the position of maximum error peaks. As Kinnear (1970) suggests, this mode is easier to plot and tended to group errors together so that the axis was somewhat more obvious (see Figure 4).

The only patient for whom there was a substantial difference between Farnsworth and Kinnear plots put one cap at the end of the box rather than in the centre where it belonged. The cap was left over and



C.B. Left Eye 1

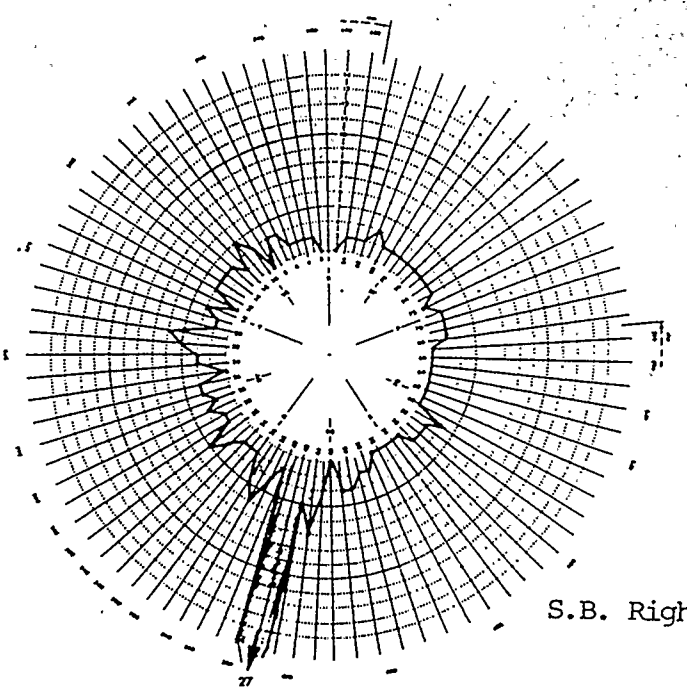


C.B. Left Eye 2

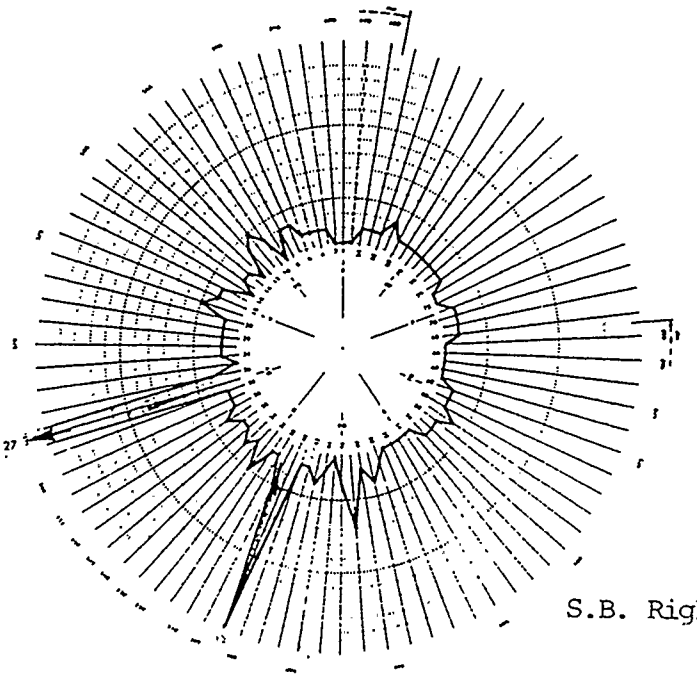
Figure 4 Farnsworth-Munsell 100-Hue Test

Circular graphs of total error scores.
1. Kinnear Mode - plotted manually
2. Farnsworth Mode - plotted by computer (Honeywell-Multic)

Both modes were very similar for most patients.



S.B. Right Eye 1



S.B. Right Eye 2

Figure 5 Farnsworth-Munsell 100-Hue Test

Circular graphs of total error score for S.B.

1. Kinnear Mode
2. Farnsworth Mode

One extemely misplaced cap; no true axis present

she (apparently) arbitrarily put it at the end of the box. This produced different profiles by the two methods; however, neither plot could be interpreted as an axis of confusion (see Figure 5).

Subjective Evaluation of Spectral Location of Deficits: Visual inspection of the 30 charts of eyes with abnormal error scores (see Appendix Table A.6) revealed a generalized decrease in discrimination in most subjects. Slight bipolar axes, present in 19 cases, were most often tetartan (8) or scotopic (5). Thirteen subjects showed only a monopolar bulge of error. If one considers both the bipolar axes and monopolar "bulges", the majority (18) of defects involved "blue" losses (8 - tetartan, 6 - tritan, 4 - atypical blue-yellow), 8 were red-green, 6 were scotopic, 5 were without defined spectral area of loss, and 8 demonstrated more than one affected axis or monopolar bulge.

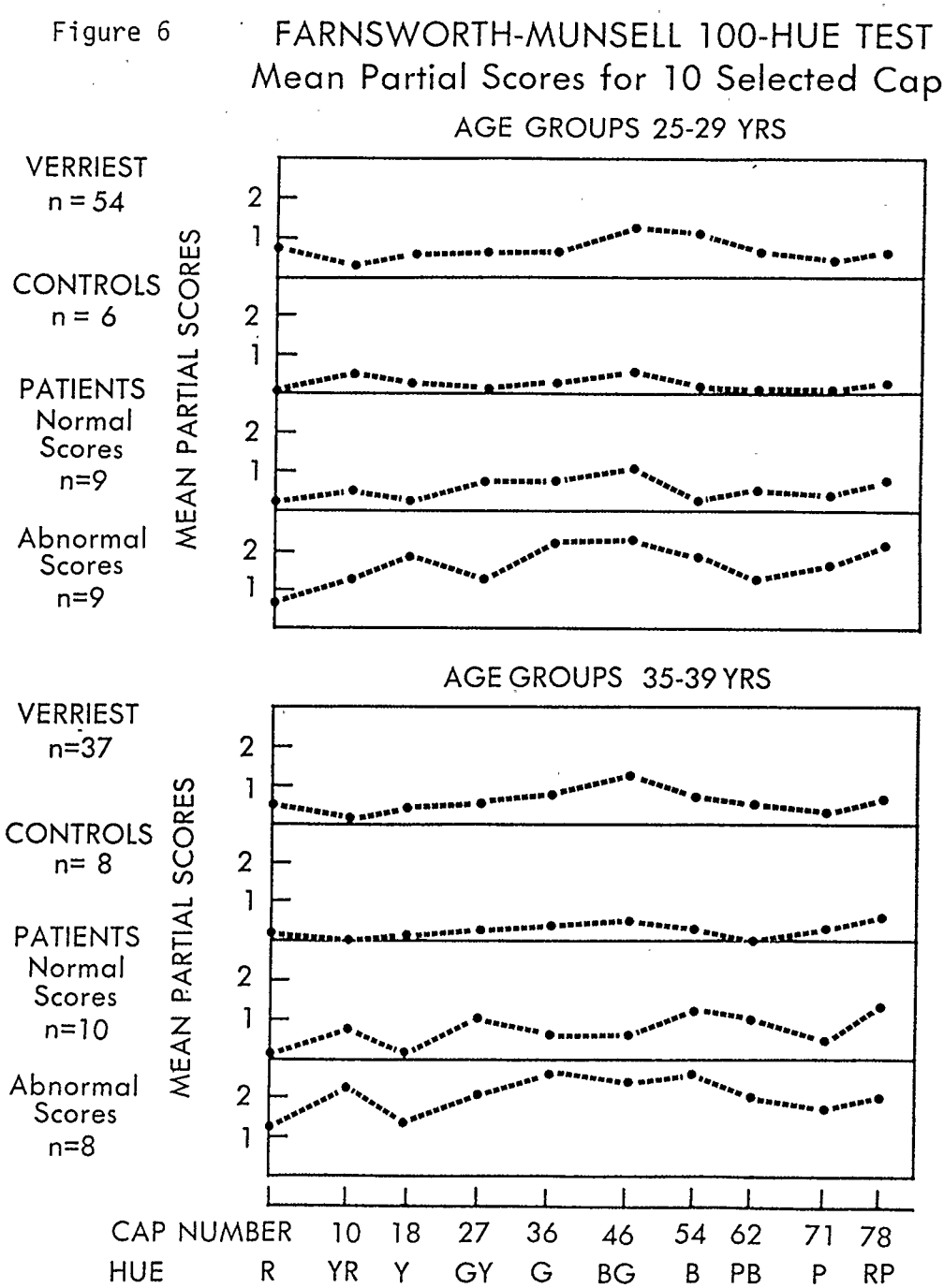
Objective Evaluation of Spectral Location of Deficits: A mathematical or statistical method for analyzing the distributions of FM 100-Hue error scores might be expected to localize spectral regions of loss more accurately. Parker (1979) has proposed a method that uses five weighted bipolar functions representing protan, deutan, tritan, tetartan, and scotopic deficits. With the programming assistance of Mr. David Orford, Parker's method was adapted to the Honeywell-Multics computer system and used to re-evaluate 30 "abnormal" error scores which had been assessed previously by visual inspection of the circular diagrams. In most cases (24/30 or 80%) the two methods gave the same

or similar axes (see Appendix Table A.6). However, the computer profile consistently suggested a more definite axis than was evident on visual inspection.

Linear Graphs: To further investigate which area of the spectrum was affected, mean partial scores were plotted for the following 10 caps representing the hues identified for selected positions on the FM 100-Hue circular diagram; cap 1 - red, cap 10 - yellow/red, cap 18 - yellow, cap 27 - green/yellow, cap 36 - green, cap 46 - blue/green, cap 54 - blue, cap 62 - purple/blue, cap 71 - purple, cap 78 - red/purple. The data were plotted in five-year age categories for five groups; three patient groups: (a) those with normal FM 100-Hue scores, (b) those with abnormal FM 100-Hue scores, and (c) the total group of patients in each category; and two control groups: (d) Verriest's data and (e) our own control data (see Figure 6 for examples).

Verriest's data plotted in this manner suggest a "W" profile with a maximum central peak (indicating the highest mean partial score and therefore most errors) occurring in the blue/green area of the spectrum with lower peaks on either end in the red area. With increasing age the pattern remains similar but the peaks become progressively larger, particularly in the central blue/green area. Our control subjects show a similar profile as do most age categories of patients with normal error scores. The "W" appearance of the profile is not as pronounced in the M.S. patients with normal error scores as in the control groups (Verriest's and our own). There is a broadening

Figure 6


FARNSWORTH-MUNSELL 100-HUE TEST
Mean Partial Scores for 10 Selected Caps
AGE GROUPS 25-29 YRS
VERRIEST
n = 54
CONTROLS
n = 6
PATIENTS
Normal
Scores
n=9
Abnormal
Scores
n=9
MEAN PARTIAL SCORES
2
1
AGE GROUPS 35-39 YRS
VERRIEST
n=37
CONTROLS
n= 8
PATIENTS
Normal
Scores
n=10
Abnormal
Scores
n=8
CAP NUMBER 10 18 27 36 46 54 62 71 78
HUE R YR Y GY G BG B PB P RP

of the blue-green peak to include blue or green in some age groups and isolated random peaks occurring in others. In patient groups with abnormal error scores the mean partial scores increase as expected. In the graphs for the second and third decade, which represent the largest numbers of subjects, the central peak has widened to include green/yellow and blue. Another peak is consistently present at cap number 10 in the yellow/red area of the spectrum.

These trends were analyzed in greater detail for the two largest groups of patients with abnormal error scores, ages 25 to 29 and 35 to 39. Mean partial scores for all 84 caps for these groups were plotted against Verriest's norms for the same groups (see Figure 7). In Verriest's groups the blue/green peak has a fairly narrow horizontal spread from cap 42 or 43, to cap 48. However, in the patient groups there is a clear expansion of the central peaks extending from caps 29 to 60 in the 25 to 29 years age group, and from caps 39 to 60 in the 35 to 39 age group.

Noticeable minima occur in these score-vs-cap (hue) functions in both age groups in the low forties, the location of the reference caps at the end of box two and beginning of box three. To examine the "Box End Effect" a frequency histogram was constructed for our control population. The number of subjects who made any errors was recorded for each of the caps (see Figure 8). There was a clear reduction in the number of errors just before or just after each reference cap. This reduction in errors near reference caps would support Taylor's (1974) suggestion for a redistribution of caps between boxes. The

Figure 7

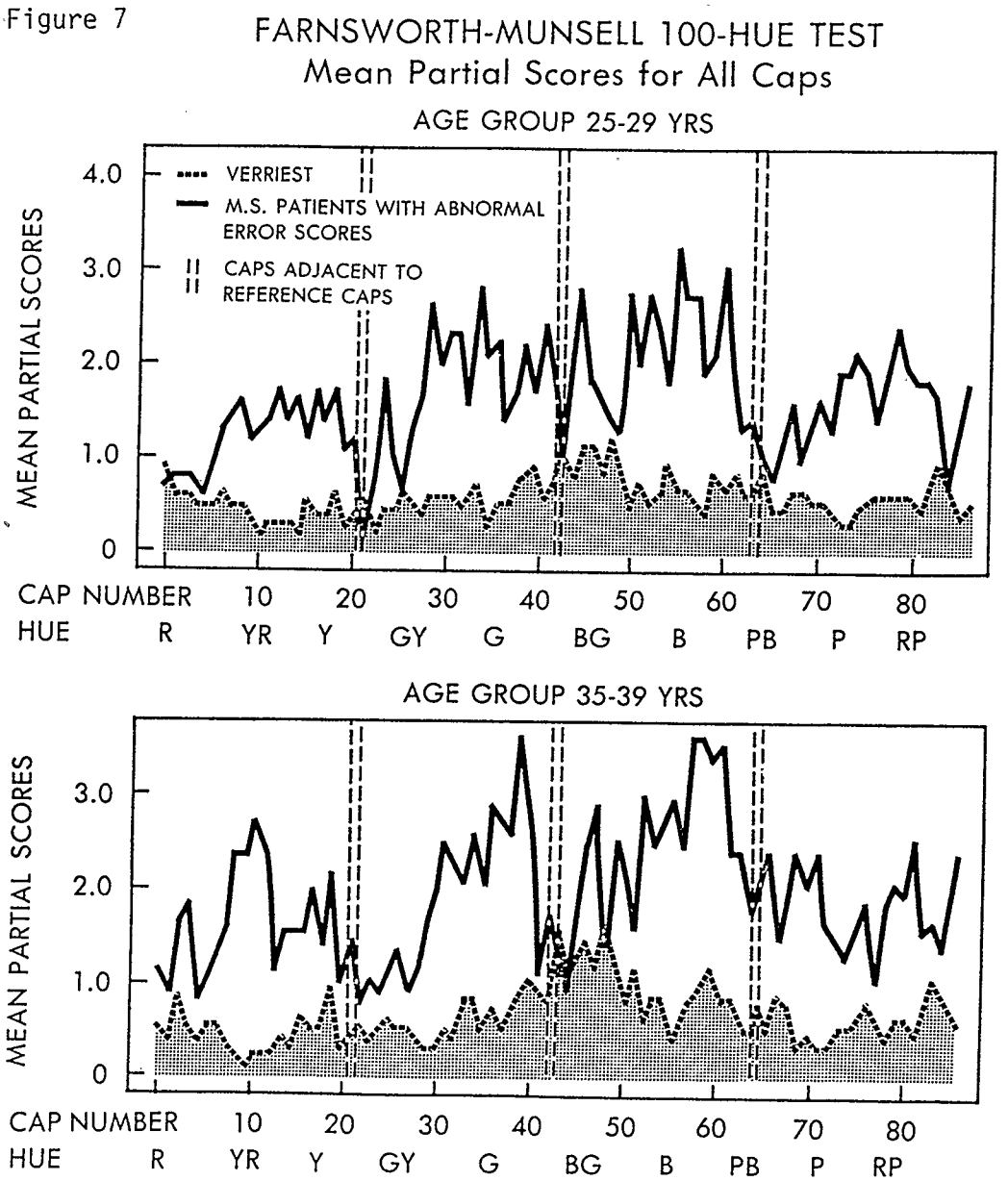
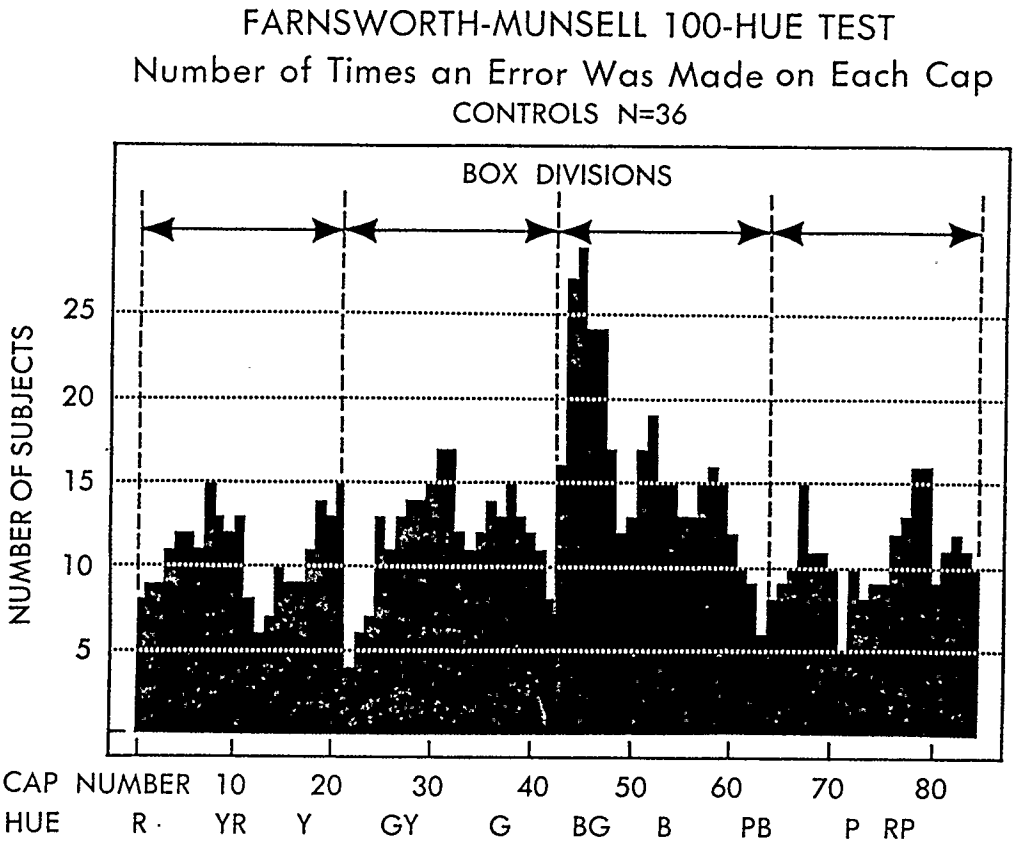

FARNSWORTH-MUNSELL 100-HUE TEST
Mean Partial Scores for All Caps
AGE GROUP 25-29 YRS
VERRIEST
M.S. PATIENTS WITH ABNORMAL ERROR SCORES
CAPS ADJACENT TO REFERENCE CAPS
MEAN PARTIAL SCORES
4.0
3.0
2.0
1.0
0
CAP NUMBER 10 20 30 40 50 60 70 80
HUE R YR Y GY G BG B PB P RP
AGE GROUP 35-39 YRS
MEAN PARTIAL SCORES
3.0
2.0
1.0
0
CAP NUMBER 10 20 30 40 50 60 70 80
HUE R YR Y GY G BG B PB P RP

Figure 8


FARNSWORTH-MUNSELL 100-HUE TEST
Number of Times an Error Was Made on Each Cap
CONTROLS N=36
BOX DIVISIONS
NUMBER OF SUBJECTS
25
20
15
10
5
CAP NUMBER 10 20 30 40 50 60 70 80
HUE R YR Y GY G BG B PB P RP

present arrangement of cap numbers 85 to 21 in box one, 22 to 42 in box two, 43 to 63 in box three and 64 to 84 in box four, puts the known axes of confusion for protan, deutan, scotopic, tritan and tetartan defects very close to reference caps. Taylor proposes a rearrangement with caps 7 to 27 in box one, caps 28 to 48 in box two, caps 49 to 69 in box three and caps 70 to 6 in box four, since this would put the central chips for the five confusion axes of protan, deutan, tritan, tetartan and scotopic through the centre rather than the edges of the boxes. However this may not be the answer for investigating acquired color vision anomalies. This study suggests that the most artefact-free analysis of M.S. patients requires a double box with caps, 25 to 65 uninterrupted by reference caps.

3.1.3 Data Analysis

3.1.3.1 Total Number (and %) of Patients with Color Vision Defects

Although half of the patients tested (20/40) reported AO-HRR plate number three incorrectly (one or both eyes), the majority of these subjects (17 of 20) also made errors on Ishihara plates and the FM 100-Hue test. I did not feel that an incorrect response on plate number three alone was sufficient to diagnose a person as color-deficient. It is interesting to note however that two of three patients who failed only the AO-HRR plates also had a delayed visual evoked response and optic neuritis in the same eye. A color deficit

was assumed if:

1. A subject reported two or more of the first 16 Ishihara plates incorrectly in one or both eyes (45% of patients, 10% of controls); or
2. A subject had an abnormally high age-correlated error score in one or both eyes, or an interocular difference in error scores greater than 45 (50% of patients, 11.5% of controls).

By these criteria 67.5 percent of patients and 18.5 percent of controls demonstrated defective color vision.

3.1.3.2 Patient Group Profiles

The majority of patients in this study had an M.S. classification of clinically definite (55%), or probable (35%); most had little or no disability (60% KO-K2); 70 percent had evidence of optic neuritis and 67.5 percent had color vision defects in one or both eyes.

Patients Grouped by VEP Results (Table 3)

The VEP results were the orginal criterion for patient selection. The most severely affected category of patients was in Group 2B - those patients with extremely prolonged VEP latencies in both eyes. All of the patients diagnosed as progressive probable were in this group as were most patients with more severe disabilities (9/15 patients indicated K5-K7 disability). The majority of patients in this

Table 3 Patient Grouping by VEP Category - demonstrating amount of physical disability and visual impairment (color vision defects and/or optic neuritis)

VEP Group	Diagnosis	N	Disability	N	Optic Neuritis	N	Color Vision Deficit*	N
1 VEP Normal one eye delayed one eye	Clin. definite	8	KO-K2	12	Eyes	14/28	ISH only	3
	Early probable	4	K3	1	Patients	11/14	FM only	5
N = 14 patients	Prog. possible	1	K7	1			Both	2
(28 eyes)	Suspected	1					Total	10
2A VEP Slight delay both eyes	Clin. definite	4	KO-K2	4	Eyes	6/8	FM only	1
					Patients	3/4	Both	2
P_1 = 118-129 m.sec							Total	3
N = 4 patients (8 eyes)								
2B VEP Long delay both eyes	Clin. definite	7	K1-K2	4	Eyes	23/30	ISH only	3
	Prog. probable	7	K3	2	Patients	13/15	FM only	3
P_1 > 130 m.sec	Prog. possible	1	K5-K7	9			Both	4
N = 15 patients (30 eyes)							Total	10
3 VEP Normal both eyes	Clin. definite	3	K1-K2	4	Eyes	1/14	FM only	2
	Early probable	3	K3-K4	3	Patients	1/7	Both	2
P_1 < 116 m.sec	Prog. possible	1					Total	4
N = 7 patients (14 eyes)								
TOTAL PATIENTS	Clin. definite	22	KO-K2	24	Eyes	44/80	ISH only	6
N = 40	Early probable	7	K3-K4	6	Patients	28/40	FM only	11
	Prog. probable	7	K5-K7	10			Both	10
	Prog. possible	3					Total*	27
	Suspected	1						

* Patients with color vision deficits in one or both eyes.
ISH only = Failed Ishihara plates only
FM only = Failed FM 100-Hue test only
Both = Failed both Ishihara plates and FM 100-Hue test.

group had optic neuritis, 76 percent of eyes in 86 percent of subjects. Group 3, patients with normal VEP's, had the least evidence of optic neuritis - 17 percent of patients, but still a significant proportion of color vision defects - 57 percent.

Patients Grouped by Diagnosis (Table 4)

Patients were regrouped according to their clinical diagnosis. Of the clinically definite patients (22/40), most had little or no physical disability (73% KO-K2); in one or both eyes tested there was a high proportion of optic neuritis (86%), VEP abnormalities (81%), and color vision defects (73%). The early probable patients (7/40) were less affected, with all having KO to K2 disability and a lower incidence of visual abnormalities (29% optic neuritis, 43% abnormal VEP, 57% color vision defects). The most severely affected were those patients classified as progressive probable. This group included the most severely disabled patients (86% K5-K7) with a high incidence of visual disturbances (optic neuritis 86%, VEP abnormalities 100%, and color vision defects 71%).

3.1.3.3 Cross-Correlation of Tests

A cross correlation of test results was performed to investigate the relationship between various tests of visual function. The results were examined first as number of eyes shown to be normal versus

Table 4 Patient Grouping by Clinical Diagnosis - Demonstrating Amount of Physical Disability and Visual Impairment (VEP Delays, Color Vision Defects and/or Optic Neuritis)

Diagnosis	# Patients	Mean Age	Disability			Optic Neuritis	VEP Delay	Abnormal Color Vision			
			K0-2	K3-4	K5-7			ISH	FM	BOTH	TOTAL
Clinically Definite	22	30	16	3	3	19	18	3	8	5	16
Early Probable	7	34	7	0	0	2	4	2	2	0	4
Progressive Probable	7	40	0	1	6	6	7	1	0	4	5
Progressive Possible	3	37	0	2	1	0	2	0	1	1	2
Suspected	1	42	1	0	0	1	1	0	0	0	0
TOTAL (Patients)	40	33	24	5	10	28	30				27

ISH = Failed Ishihara Plates only

FM = Failed Farnsworth-Munsell only

BOTH = Failed both tests.

abnormal for each condition. Table 5 displays this information in a series of 2 x 2 tables relating the VEP findings for all MS patients to the results on color vision testing and a history of optic neuritis. It also provides the chi-square statistical test for evaluating independence between variables. The null hypothesis was that the results of the VEP and the other tests evaluated varied independently. This hypothesis appears valid for the VEP paired with any of the color vision tests. However, it is rejected for the VEP versus optic neuritis, suggesting that these two indicators are related. The relationship between these same tests was also examined by calculating the percentage of eyes for which results were correlated, i.e. both tests were normal or abnormal (Table 6). This information is subdivided into the various patient groups determined according to VEP latency. As expected from the chi square distribution (Table 5), in the 'total patient' group there is a higher correlation between an abnormal VEP and a history of optic neuritis (74%) than between an abnormal VEP and color vision deficits determined with AO-HRR, Ishihara or FM 100-Hue tests.

Table 7 explores the relationship between optic neuritis and performance on color vision tests. The chi-square distribution suggests that performance on the AO-HRR test is related to evidence of optic neuritis but that performance on the Ishihara or the FM 100-Hue test is independent of optic neuritis.

Table 5 Cross Correlation: Chi Square Test.
VEP Results versus Results of Color Vision Testing and Optic Neuritis. Total Group of M.S. Patients, N = 80 Eyes.

		VEP		Chi Square	
		Normal	Abnormal	X^2	Significance
Optic Neuritis					
Signs, symptoms and/or optic atrophy	No (normal)	22	13	17.07	p<0.005
	Yes (abnormal)	8	37		
AO-HRR					
one or more missed /6 screening plates	Normal	22	31	0.50	0.1<P<0.95
	Abnormal	9	18		
Ishihara					
Abnormal = 2 or more missed / first 16 plates	Normal	22	30	1.5	0.1<P<0.95
	Abnormal	8	20		
FM 100-Hue					
Abnormal = total error score above age norm	Normal	21	29	1.2	0.1<P<0.95
	Abnormal	9	21		

null hypothesis (Ho) variables are independent.
Accept Ho for VEP versus AO-HRR, Ishihara and FM 100-Hue.
Reject Ho for VEP versus optic neuritis (i.e. these two variables appear to be related).

Table 6 Cross-Correlation: VEP results versus results of color vision testing and optic neuritis (patients grouped by VEP latency results)

	Group 1 N = 28	Group 2A N = 8	Group 2B N = 30	Group 3 N = 14	Total Patients N = 80
Optic Neuritis and VEP Correlated*	61%	75%	77%	93%	74%
AO-HRR and VEP Correlated*	64%	50%	33%	57%	50%
Ishihara and VEP Correlated*	57%	37.5%	57%	71%	52.5%
FM 100-Hue and VEP Correlated*	54%	50%	57%	71%	52.5%

Group 1 VEP - normal one eye
Delay one eye

Group 2A VEP - both eyes
Slight delay

Group 2B VEP both eyes
Long delay

Group 3 VEP - both eyes
Normal

* Correlation = normal on both tests or abnormal on both tests.

Table 7 Cross Correlation: Optic Neuritis Versus Color Vision Tests

	Optic Neuritis		Chi Square		% of Time Tests
	No (Normal)	Yes (Abnormal)	X^2	Significance	Correlated
AO-HRR					
Normal	30	5	9.4	$p<0.005$	64%
Abnormal	24	21			
Ishihara					
Normal	23	12	0.01	$0.1<p<0.95$	49%
Abnormal	29	16			
FM 100-Hue					
Normal	22	12	0.02	$0.1<p<0.95$	49%
Abnormal	29	17			

Correlations = normal on both tests or abnormal on both tests.

3.2 ANOMALOSCOPE STUDY RESULTS

3.2.1 Repeated Farnsworth-Munsell 100-Hue Test

On the repeated FM 100-Hue test, administered on the day of anomaloscope examination, error scores were abnormal for three patients in both eyes, that is 30 percent of eyes and patients were abnormal. The mean total error score for the six affected eyes was 180, and mean patient age was 28 years. The errors appeared as a generalized reduction in wavelength discrimination on the polar diagram of the FM score sheet. Table 8 suggests a tendency for a protan or deutan monopolar bulge in charts for eyes with a history of optic neuritis and a slight scotopic or tetaratan bulge in charts for patients without optic neuritis, but these axes were not distinct.

Figure 9 illustrates that the mean partial scores for the M.S. patients (with abnormal total error scores) are clearly much higher than the error scores for normal subjects. No single area of the spectrum is particularly affected, although the mean error score for the M.S. patients is highest in the blue region.

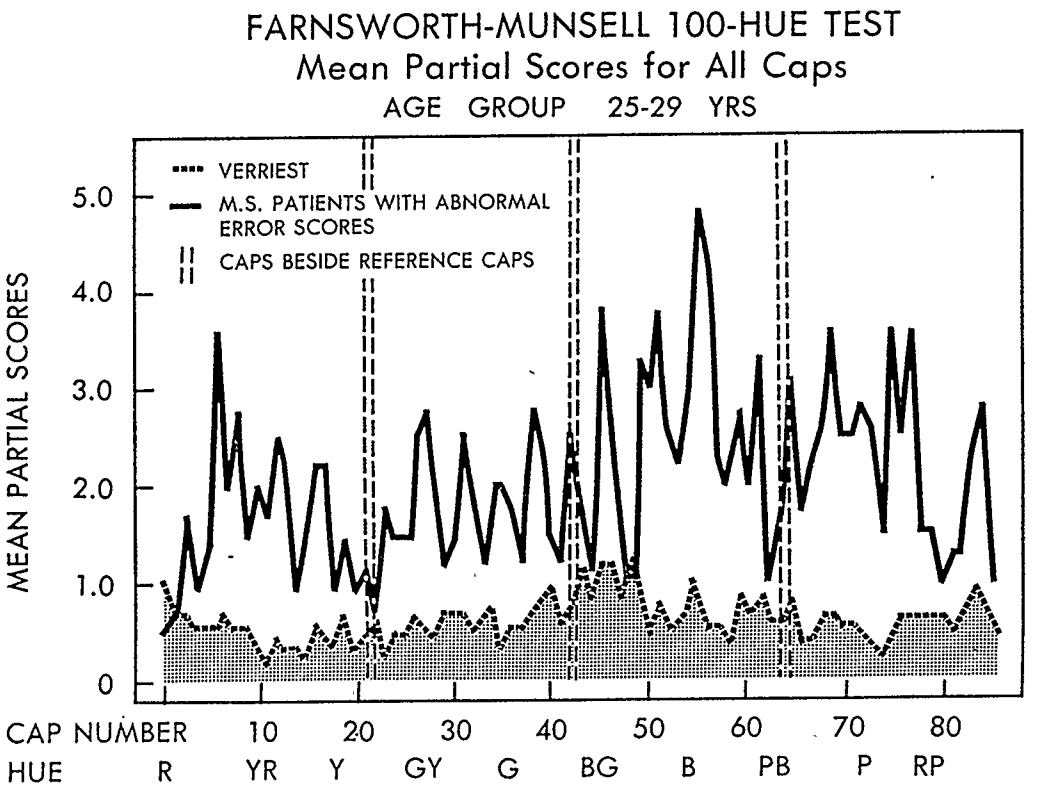
Three other patients had demonstrated abnormal FM 100-Hue test scores in one eye on a previous examination, but achieved normal error scores when retested on the same day as the anomaloscope examination.

Table 8 Farnsworth-Munsell 100-Hue Test:
(Repeated for anomaloscope study)

Patient	Age	Eye	Optic Neuritis	F.M. Score	Axis* (Mid Point Cap #)
E.R.	27	R	Yes	200	Slight protan monopolar bulge (66)
		L	No	162	Slight scotopic monopolar bulge (12) Slight tetartan monopolar bulge (76)
M.S.	28	R	No	175	General
		L	Yes	157	Slight deutan monopolar bulge (58)
M.B.	32	R	Yes	153	Slight atypical protan monopolar bulge (69)
		L	No	237	General

* All patients demonstrated a generalized reduction in wavelength discrimination. Axes were not distinct.

Figure 9


FARNSWORTH-MUNSELL 100-HUE TEST
Mean Partial Scores for All Caps
AGE GROUP 25-29 YRS
VERRIEST
M.S. PATIENTS WITH ABNORMAL ERROR SCORES
CAPS BESIDE REFERENCE CAPS
MEAN PARTIAL SCORES
5.0
4.0
3.0
2.0
1.0
0
CAP NUMBER 10 20 30 40 50 60 70 80
HUE R YR Y GY G BG B PB P RP

3.2.2 Pickford-Nicolson Anomaloscope Results in M.S. Patients

3.2.2.1 Norms

The norms used to evaluate the anomaloscope results were those published by Lakowski (1971), since the same examiner used the same instrument for this study. Prior to testing our sample of M.S. patients, Dr. Lakowski tested nine subjects without M.S. to familiarize this author (A. Harrison) with the use of the anomaloscope. Two of the subjects had documented congential color deficiencies which were characterized as protanopic on the anomaloscope. The remaining 'test' group consisted of five subjects in the 26 to 35 year age group (one of whom was tested binocularly), one subject in the 36 to 45 year age group (whose performance on the FM 100-Hue test had been abnormal previously) and one subject in the 45 year plus age group. The mean data for this group are included for interest (Table 9). Although the mean matching ranges for this group are within or very close to the 95 percent for the 36 to 45 age category, this 'test' group is not intended as a control in the conventional sense.

3.2.2.2 Quantitative Assessment of Losses

The P-N anomaloscope revealed color vision losses in a signficant proportion of individuals in our M.S. sample: 13 of 20 eyes in seven of 10 patients (see Appendix Table A.7). All patients with

Table 9 The Pickford-Nicolson Anomaloscope: Chromatic Discrimination Mean Matching Ranges for M.S. Patients, Published Norms and Test Groups

	Patient Group		
			Total
Age	26-35	36-45	27-42
Number (eyes)	n=12	n=6	n=18
Equation			
	mean(S.D.)	mean(S.D.)	Mean(S.D.)
red-green	11.9(±9.6)	23.3(±24.5)	15.7(±16.3)
yellow-blue	29.2(±15.8)	52.3(±43.0)	36.9(±28.9)
green-blue	24.2(±19.4)	47.3(±45.3)	39.8(±31.2)

	Published Norms (Lakowski 1971)		Test Group
Age	26-35	36-45	27-56
Number (eyes)	n=33	n=24	n=13
Equation			
	mean(95%)	mean(95%)	mean(S.D.)
red-green	2.8(±6.8)	3.0(±7.0)	4.1(±2.7)
yellow-blue	5.9(±12.5)	7.0(±18.0)	18.2(±13.6)
green-blue	5.3(13.5)	6.0(16.0)	16.5(±17.8)

losses had extended anomaloscope matching ranges indicating impaired chromatic discriminative ability. More than half of those affected (8/13 eyes in 5/7 patients) also had a disturbance in the mid-matching point suggesting a shift in the normal balance between the chromatic pathways involved in the affected equation.

As a group (excluding data from the patient with acute optic neuritis), M.S. patients demonstrated considerably larger mean matching ranges than normal: four to five times larger than those norms for the 26 to 35 year age group and seven to eight times larger than those norms for the 36 to 45 year group (see Table 9). These differences were significant at the 0.01 level (two-tailed t-test).

3.2.2.3 Spectral Characteristics of Losses (See Appendix Table A.7)

All patients with chromatic discriminative losses (matching range abnormalities) demonstrated disturbances in the blue-yellow equation (13/13 eyes), most also had an abnormal blue-green equation (10/13 eyes), and about half also indicated changes in the red-green equation (7/13 eyes). Some patients with abnormal matching ranges demonstrated normal mid-matching points, but there were no patients with disturbances in mid matching points who demonstrated normal matching ranges. As with the matching ranges, all patients with mid-matching abnormalities demonstrated disturbances in the blue-yellow equations (7/9 eyes), but only about a third of those affected had blue-green abnormalities (3/9 eyes) and/or red-green abnormalities (4/9 eyes).

3.2.2.4 Brightness Abnormalities

Two patients demonstrated a most unusual brightness response, which seemed somewhat analogous to the 'recruitment' phenomenon in audiology. Increasing quantities of light would be requested to perform a match; then a threshold seemed to be reached and the patient would object to the excessive brightness she had requested a few moments before. Both patients with this rather bizarre response had extensive losses in chromatic discrimination and disturbed mid-matching points, with the red-green equation somewhat less affected than the 'blue' equations.

3.2.2.5 Anomaloscope Discrimination in 'Acute' Optic Neuritis

Performance on the anomaloscope was extemely abnormal in the one patient with acute optic neuritis (see Table 10). The results for B.C. are considered separately because of a past history of optic neuritis in both eyes and an acute optic neuritis in her right eye on the day of the anomaloscope examination. Because of very poor acuity (3/200), her right eye was tested with the large field (5 cm) at close range (1/3 meter rather than the usual 1 meter) representing a visual angle of about 9°. For her left eye the usual viewing aperture (visual angle of 1 1/2°) was used. The anomaloscope matching ranges for her left eye (with a history of optic neuritis) were approximately six times greater than normal for the red-green and green-blue equations and nine times

Table 10 The Pickford-Nicolson Anomaloscope:
Chromatic Discrimination in Acute Optic Neuritis

Equations	Matching Ranges			
	B.C.* Age 39 Years		Published Norms (Lakowski 1971) Age 36-45 Years	
	RE	LE	Mean	95%
Red-green	72	20	3.0	7.0
Yellow-blue	118	69	7.0	18.0
Green-blue	103	40	6.0	16.0

* M.S. Patient with previous history of bilateral optic neuritis who had an acute optic neuritis in her right eye on the day she was tested with the anomaloscope. VA. RE 3/200; LE 20/20

greater for the yellow-blue. For her right eye (with acute optic neuritis) the ranges were 17 times larger than normal for green-blue and yellow-blue and 24 times larger for the red-green equations.

3.2.2.6 Anomaloscope Discrimination in 'Stable' Optic Neuritis

In the other M.S. patients investigated, a past history of optic neuritis or evidence of optic atrophy, did not affect chromatic discrimination on the anomaloscope as dramatically as did acute optic neuritis (see Table 11). In the 26 to 35 year age group the mean matching ranges for the yellow-blue and green-blue equations are similar for patients with or without optic neuritis. In the 36 to 45 year age group the mean matching ranges for patients with optic neuritis are higher than for those without optic neuritis: approximately one and one half times greater for the yellow-blue and green-blue equations and two times greater for the red-green equation. These differences are not statistically significant even at the $\alpha = 0.1$ level with a one-tailed t-test. In the 26 to 35 year age group there is a statistically significant difference between the mean matching ranges of those patients with optic neuritis and those without optic neuritis (two-tailed t-test, $\alpha = 0.1$, assuming population variances unequal) for the red-green equation only.

Table 11 The Pickford-Nicolson Anomaloscope: Chromatic Discrimination Mean Matching Ranges for M.S. Patients, With and Without 'Stable' Optic Neuritis

	With Optic Neuritis		
	Age Range		
	26-35	36-45	Total
	n=6	n=3	n=9
Mean Age	29.2	39.7	32.6
Mean VEP	136.2	131.3	134.6
100-Hue Mean Total Scores	115	93	108
Anomaloscope Matching Range (Discrimination)			
	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)
red-green	17.0(±12.1)	32.0(±29.5)	22.0(18.9)
yellow-blue	28.7(±16.4)	61.3(±51.6)	39.6(±32.6)
green-blue	26.3(±20.2)	54.3(±45.1)	35.6(±31.0)

	Without Optic Neuritis		
	Age Range		
	26-35	36-45	Total
	n=6	n=3	n=9
Mean Age	29.2	39.7	32.6
Mean VEP	114.3	113.3	114.0
100-Hue Mean Total Scores	122	82	110
Anomaloscope Matching Range (Discrimination)			
	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)
red-green	6.8(±1.9)	14.7(±20.2)	9.4(±10.0)
yellow-blue	29.7(±16.8)	43.3(±43.2)	34.2(±26.3)
green-blue	22.0(±20.2)	40.3(±54.4)	28.1(32.8)

3.2.3 Data Analysis

3.2.3.1 Cross-Correlations Between Tests of Visual Function

In our M.S. patients, a history of optic neuritis was positively correlated with prolonged VEP latency and impaired performance on the red-green equation of the anomaloscope (Table 12). Consistent with our previous findings, using a chi-squared distribution assuming a null hypothesis of independent variables, there was a highly significant correlation ($p = 0.01$) between a history of optic neuritis and an abnormal VEP latency. This same test suggests that neither failure on the FM 100-Hue test nor overall failure on the anomaloscope (taking into consideration all three equations) was related to a history of optic neuritis. On the individual anomaloscope equations, however, there was a weak correlation ($p = 0.1$) between abnormal performance on the red-green equation and a history of optic neuritis.

There was no correlation between VEP latency and performance on either the FM 100-Hue test or the yellow-blue anomaloscope equation (Table 13) There was a weak correlation ($p \approx 0.1$) between VEP latency and the red-green equation and a somewhat greater correlation ($0.05 < p < 0.1$) between VEP latency and the green-blue anomaloscope equation.

Table 12 Cross-Correlation Between a History of Optic Neuritis and the Results of Three Tests of Visual Function for Nine M.S. Patients (18 eyes)

	VEP Latency		FM 100-Hue Error Scores		Anomaloscope Matching Ranges: Red-Green Equation		Yellow-Blue Equation		Green-Blue Equation	
	NOR	AB	NOR	AB	NOR	AB	NOR	AB	NOR	AB
Optic Neuritis										
No	5	4	4	5	8	1	3	6	6	3
Yes	0	9	5	4	5	4	3	6	4	5
X^2*	6.92		0.22		2.8		0		0.736	
Significance	0.005<p <0.01		0.1<p <0.95		0.05<p <0.1		0.995<p		0.1<p <0.95	
Correlated	14(78%)		8(44%)		12(67%)		9(50%)		11(61%)	
Not Correlated	4(22%)		10(55%)		6(33%)		9(50%)		7(39%)	

Table 13 Cross-Correlation Between VEP Latency and Color Vision for Nine M.S. Patients (n = 18 eyes)

	FM 100-Hue Error Scores		Anomaloscope Matching Ranges: Red-Green Equation		Yellow-Blue Equation		Green-Blue Equation	
	NOR	AB	NOR	AB	NOR	AB	NOR	AB
VEP Latency								
Normal	3	2	5	0	3	2	5	0
Abnormal	9	4	8	5	6	7	7	6
X^2*	0.138		2.663		0.031		3.46	
Significance	0.1<p <0.95		p≈0.1		0.1<p <0.95		0.05<p <0.1	
Correlated	7(39%)		10(56%)		10(56%)		14(61%)	
Not Correlated	11(61%)		8(44%)		8(44%)		7(39%)	

* Null Hypothesis = variables are independent
correlated = both tests are normal or both tests are abnormal

3.3.2.2 Chromatic Discrimination Losses Measured on the Anomalscope in M.S. Patients and Patients with Raised Intraocular Pressure

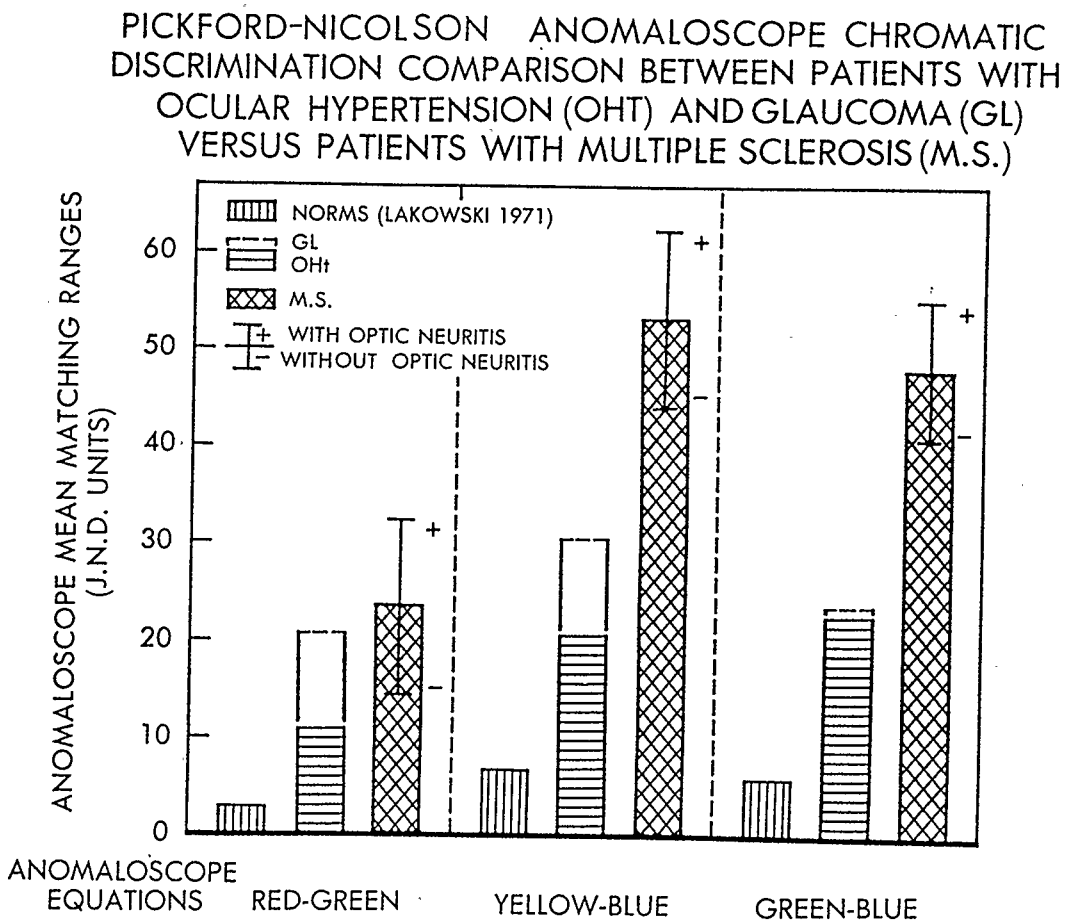
A comparison of color vision losses demonstrated with anomaloscope testing between patients with M.S. and those with raised intraocular pressure was undertaken to elucidate where the losses might occur in M.S. patients.

Figure 10 demonstrates the relative losses in chromatic discrimination as indicated by expanded mean matching ranges on the three anomaloscope equations. By visual inspection (or comparing the values in Tables 9, 10 and 14) it is possible to appreciate the profound losses that occur in M.S., especially in the 'blue' equations. In ocular hypertension the mean matching ranges are approximately three times the norms for all three equations. In all equations the M.S. chromatic losses are somewhat greater in patients with optic neuritis than in those without optic neuritis, however these differences are most pronounced for the red-green equation. A precise comparison with the losses which occur in glaucoma cannot be made because of the small pupil size in the glaucoma patients, which might tend to reduce their discrimination (i.e. increase their mean matching ranges) (Lakowski and Oliver 1974). However the mean matching ranges for the glaucoma patients have been ghosted in Figure 10 to emphasize the severity of the M.S. losses. With a normal pupil, glaucoma mean matching ranges would not be larger, they would be smaller. However even with the abnormally large mean matching ranges, the losses are still approximately twice as great in M.S. compared with glaucoma, for the yellow-

Table 14 The Pickford-Nicolson Anomaloscope: Chromatic Discrimination in Patients with Raised Intraocular Pressure - P-N Anomaloscope Mean Matching Ranges and Standard Deviations

	Ocular Hypertension Natural Pupil Mean Age 43.7 Years n = 7 eyes		Glaucoma Miotic Pupil Mean Age 36.1 Years n = 11 eyes	
Equations	Mean	Standard Deviation	Mean	Standard Deviation
Red-green	10.6	5.0	20.8	30.8
Yellow-blue	20.3	9.2	30.3	32.6
Green-blue	22.3	10.8	22.7	28.6

Figure 10


PICKFORD-NICOLSON ANOMALOSCOPE CHROMATIC DISCRIMINATION COMPARISON BETWEEN PATIENTS WITH OCULAR HYPERTENSION (OHT) AND GLAUCOMA (GL) VERSUS PATIENTS WITH MULTIPLE SCLEROSIS (M.S.)
ANOMALOSCOPE MEAN MATCHING RANGES (J.N.D. UNITS)
NORMS (LAKOWSKI 1971)
GL
OHt
M.S.
WITH OPTIC NEURITIS
WITHOUT OPTIC NEURITIS
0
10
20
30
40
50
60
+
−
ANOMALOSCOPE EQUATIONS
RED-GREEN
YELLOW-BLUE
GREEN-BLUE

blue and the blue-green equations. The losses in glaucoma patients and M.S. patients are only of the same order for the red-green equation.

4. DISCUSSION

4.1 CHARACTERIZATION OF COLOR VISION LOSSES IN M.S. PATIENTS WITH CONVENTIONAL CLINICAL TESTS

The initial investigation to assess color vision performance in M.S. patients with conventional clinical tests resulted in three major findings.

1) Color vision losses were demonstrated in a significant proportion of M.S. patients: 50 percent of patients tested with the Farnsworth-Munsell 100-Hue test (FM 100-Hue test), 45 percent tested with Ishihara Plates, and 67.5 percent if the results of both tests were considered.

2) The profile of color vision disturbances evident on the FM 100-Hue test differed from that normally associated with optic neuritis. Some investigators have suggested that defects in color vision which occur in optic neuritis consist of losses in wavelength discrimination along the red-green axis accompanied by a "normal spectral curve of relative luminosity efficiencies" (a type II red-green defect, Verriest 1963). In this study, with the FM 100-Hue test, the defect presented as a generalized loss in wavelength discrimination, particularly in the blue area of the spectrum.

3) The color vision abnormalities occurred in patients with multiple sclerosis regardless of whether or not they had a past history or persistent evidence of optic neuritis. In our study, 44 of 80 eyes, in 28 of 40 patients, had optic atrophy or a history of optic neuritis.

Published statistics of the relationship of optic neuritis to multiple sclerosis vary widely (Kirkham and Coupland 1981; Chiappa 1980), and this issue is not addressed here. What is more significant is the positive statistical correlation between optic neuritis and visually evoked potentials. This finding agrees with numerous other studies (Halliday et al. 1977; Celesia 1978; Asselman et al. 1975), and supports our diagnosis of optic neuritis. Although there was a highly significant positive correlation between a history of optic neuritis and an abnormal VEP, there was no such correlation between a history of optic neuritis and color vision abnormalities revealed by the FM 100-Hue test or the Ishihara plates. Color vision defects and optic neuritis were correlated in about 50 percent of cases. As expected, a chi-square analysis confirmed that there was a very high probability that this correlation could have occurred by chance.

4.2 CHROMATIC DISCRIMINATION LOSSES IN M.S. WITH ANOMALOSCOPE TESTING

The most dramatic finding in this second segment of the study was the high percentage (70%) of M.S. patients who demonstrated significant losses in yellow-blue discrimination on the anomaloscope, regardless of whether or not there was a history of optic neuritis or an abnormal VEP latency. Other researchers have found red-green losses in M.S. patients with optic neuritis (Verriest 1963; Cox 1961). Our conclusions agree with theirs. Despite admitted difficulties in diagnosing optic neuritis unless it is in the acute phase, there does

appear to be a positive correlation between a history of optic neuritis, an increased VEP latency and a red-green color vision anomaly. However, in addition, many M.S. patients have severe yellow-blue losses independent of any history or evidence of optic neuritis.

4.3 Chromatic Discrimination Losses with Anomaloscope Testing in Patients with M.S. and in Patients with Raised Intraocular Pressure

The visual deficits which occur in glaucoma are probably due to retinal ganglion cell damage. Therefore a comparison of losses in chromatic discrimination between patients with M.S. and those with raised intraocular pressure was undertaken to elucidate the possible anatomical locations of damage which might cause color vision losses in M.S. patients.

There has been discussion regarding the location of the primary insult in chronic glaucoma (disc versus retina) and the primary mechanism of the damage (ischemic versus mechanical) (Duke-Elder, 1969; Anderson 1975). Many authors indicate that the nerve fibre damage is due to interference with the perfusion of blood at the nerve head (Drance 1972). An intriguing hypothesis was proposed suggesting that the vascular compression might be secondary to the collapse of the glial support structure (Anderson 1975). However, subsequent histological examination suggests that the nerve fibres are damaged at the scleral lamina cribrosa by local blockage of axonal transport (Quigley, Addick and Green 1981).

Regardless of the many points of controversy, it appears that in glaucoma there is optic nerve and optic disc damage. The resulting impairment of retinal ganglion cell function may be evident by visual field changes and/or visual acuity defects. There is also evidence of significant losses in chromatic discrimination both in glaucoma and the less severe ocular hypertension (Lakowski, Bryett and Drance 1975).

Figure 10, page 86 (see also Results Section 2.3.2) emphasizes the severity of the color vision losses which occur in M.S. patients relative to those which occur in patients with raised intraocular pressure. Figure 10 also provides a visual demonstration of the effects of retinal ganglion cell damage. It appears that red-green losses are proportionately more severe in patients with evidence of retinal ganglion cell damage (i.e., in glaucoma and M.S. with optic neuritis). Although there is also a tendency for larger losses in the 'blue' anomaloscope equations for patients with ganglion cell damage, this relationship is not as obvious as for the red-green equation.

These comparisons of data from patients with M.S. and those with raised intraocular pressure substantiate other findings in this study. In summary, the results suggest a relationship between optic neuritis, abnormalities in the VEP, retinal ganglion cell damage and losses in red-green discriminiation on the anomaloscope. There is no dispute that many M.S. patients do indeed experience symptomatic or asymptomatic episodes of optic neuritis. These studies suggest that M.S. patients may <u>also</u> have other visual system deficits, independent of optic neuritis. These "other" abnormalities result in losses in

chromatic discrimination, particularly in the blue area of the spectrum. These losses are demonstrable on the FM 100-Hue test, and on the blue-yellow and blue-green anomaloscope equations.

4.4 Color Vision Tests for the Assessment of M.S. Patients

In addition to determining the frequency and type of color vision disturbances which occur in M.S., another aim of this study was to investigate which tests appear to be most useful in the diagnosis and monitoring of patients with multiple sclerosis.

The city university test was not very useful since very few patients (2.5%) and no controls made errors on the test.

The panel D-15 was also somewhat insensitive (15% errors in the patient group) and poor at distinguishing patients from controls (11% errors in the control group). It might be possible to increase the sensitivity of the test using a desaturated version. The Lanthony desaturated Panel D-15 was designed for use with acquired color vision disturbances (Lanthony 1978a). The 15 caps are paler and lighter (lower chroma, higher value) than the conventional panel D-15 which was designed to detect the color confusions in congenital color vision deficits.

The AO-HRR was more sensitive and better at differentiating patients from controls. Errors were made viewing with 32.5 percent of eyes in 50 percent of patients and by 3.7 percent of the control population. However in half of those who failed the test an incorrect

response on plate number 3 was the only error made. Personally, I would not feel confident in diagnosing a patient as color deficient on the basis of only one missed plate. Thus I would not recommend the AO-HRR as the sole test for assessing color vision performance. It would, however, be a useful addition to a battery of color vision tests.

In this study, using the pass/fail criteria described in Section 3.1, the Ishihara test was quite useful in detecting disturbances of color vision (31% of eyes; 45% of patients). However, further control studies are necessary to validate our pass/fail criteria. Although the Ishihara may be useful in detecting color vision anomalies it has two serious deficiencies. 1) There is no provision for assessing 'blue' deficits which we have found to occur in M.S. patients.
2) The defect cannot be reliably quantitated, making the Ishihara inappropriate for monitoring patients, particularly during therapy trials.

The F.M. 100-Hue was somewhat more sensitive than the Ishihara plates. If the results of one or both eyes are considered, 10 patients failed both tests, 6 patients failed only the Ishihara test, and 11 failed the F.M. 100-Hue test only (see Table 3). In addition to greater sensitivity than the other tests just described, the F.M. 100-Hue also allows a comprehensive quantitative and qualitative assessment of color vision disturbances, which provides a sound basis for monitoring patient progress. However, before the test can be used to monitor the progress of patients on therapy, further studies are needed to determine color vision performance with this test during the

natural course of the disease. This point must be emphasized in view of three patients who demonstrated borderline abnormal scores in one eye with an initial evaluation, but borderline normal scores when retested as part of the anomaloscope study. If a screening test has been used to rule out a congenital color vision disturbance, and the FM 100-Hue test scores are clearly higher than the age related norms, then I would feel confident in diagnosing a color vision deficiency. This finding could be used to augment the clinical diagnosis of M.S. by demonstrating visual system involvement. If, however, the FM error scores are borderline, particularly in just one eye, then perhaps the FM 100-Hue test should be repeated to confirm the color deficiency.

The Lanthony New Color Test (Lanthony 1978b) is another arrangement test, designed specifically for use in acquired color vision defects. It allows determination of neutral zones (colors confused with grey) and evaluation of discriminative ability at each of four chroma (saturation) levels. The test consists of four boxes with 15 colored caps each. The hue variations in each box represent the same 15 steps around a color circle. All caps are of equal brightness but the boxes vary in saturation. There are also 10 grey caps of increasing Munsell value. The colored caps from one box are mixed with the grey caps. The observer is requested to 1) sort the caps into two groups - one with colors only, the other with greys only (separation phase), 2) arrange the grey caps from bright to dark, and 3) arrange the remaining caps according to color (steps 2 and 3 are the classification phase). The separation phase allows determination of neutral

zones according to which colored caps are confused with greys. The classification phase allows 1) determination of relative luminosity by the position of colored caps on the grey scale and 2) assessment of chromatic discrimination according to the arrangement of the colored caps. This test was not used in our study but might be useful in future studies concerned with the clinical assessment of color vision losses in M.S. patients.

The anomaloscope was the most sensitive and versatile test used in these studies. A large number of M.S. patients (70%) demonstrated color vision disturbances when assessed with the anomaloscope. In addition, the anomaloscope also provided qualitative data which were useful for determining what type of color vision capabilities were affected, and quantitative data which allowed comparison with other studies. Unfortunately the P-N anomaloscope is not commercially available. One could build a P-N anomaloscope since the instrument is optically and mechanically straightforward. However, it requires a large control population to provide meaningful norms, and a skilled examiner.

There were clear differences in performance on the battery of color vision tests between subjects with known congenital color vision deficiencies, and M.S. patients. Subjects with congenital color vision disturbances made a great many errors on the screening tests, in some instances all responses were incorrect. Errors occurred along a red-green axis of confusion on both the screening tests, and on the FM

100-Hue test. On the FM 100-Hue test the total error scores were high but not excessively so, and in some cases the scores were even within normal age limits. In contrast, the profile of color vision losses in M.S. patients was quite different. M.S. patients with color vision losses tended to do well on the screening tests (with the exception of the Ishihara plates) but poorly in the FM 100-Hue test. In most cases the FM 100-Hue test error scores were clearly abnormal, with significant increases in total error scores. There were overall losses in wavelength discrimination particularly in the 'blue' area of the spectrum.

It is important to use more than one test to assess color vision performance in M.S. patients. A battery of tests should include at least a screening test, such as the AOH-RR plates to rule out a congenital disturbance, and a full spectrum hue discrimination test, such as FM 100-Hue to assess the severity and type of abnormality present. An additional investigation with an anomaloscope which allows a full spectrum match would be extremely valuable but may not always be possible in a clinical testing situation.

4.5 HYPOTHESES

In this section four hypotheses are discussed which might account for the results of these studies. Suggestions for further testing which might be considered to test these hypotheses are also included.

1.) The generalized loss of wavelength discrimination with color vision testing might be due to disturbances in the 'opponent' pathways in some M.S. patients. To develop this argument, some aspects of color opponency are discussed. The blue cone system is dealt with separately, for a number of reasons:

1) 'blue' losses were evident with our testing;
2) the blue cone system is unique in a number of respects, and
3) a decrement in the blue cone system may have implications for the processing of chromatic information in the 'blue versus long wavelength sensitive' opponent system.

The definition of opponency depends to some extent on the method used to investigate it: perceptual, psychological, or electrophysiological. In the electrophysiological investigation of retinal ganglion (RG) cells, the term color opponent is applied to cells which respond to light of a particular spectral composition in one way (an excitation response to a red light for example) but in a different way to a stimulus of a different spectral composition (an inhibitory response to a green light in this example). Color opponent cells also exhibit a spatial center-surround antagonism. The investigation of color opponent RG cells is further complicated by variations in response patterns which occur as a function of the temporal (as well as chromatic and spatial) characteristics of the stimulus.

Electrophysiological investigation has revealed variations in the types of color opponent retinal ganglion cells, their response functions and their retinal distribution (Zrenner 1983, pp. 20-55; de

Monasterio 1981). The type most commonly encountered was the red on-center (21%), followed by the green on-center (11%), the green off-center (9%) and the red off-center (5%). All of these cells had an antagonistic annular surround of a complementary color sensitivity. Blue on-center cells accounted for only 5.7 percent. They were antagonized by input from long-wavelength cones. Since it was not clear whether this antagonism was from both red and green cones or just red cones, this is referred to as blue-long opponency. Inhibitory blue cone input was extremely rare and only 0.3 percent of ganglion cells sampled were blue off-center.

There is tremendous variation in the action spectra of red-green opponent cells. There appears to be an almost continuous gradation in the relative inputs of the center and surround mechanisms. This varies from almost total dominance by the center, to equal center-surround input, to almost total domination by the surround. Thus even under fixed stimulus conditions with diffuse illumination the neutral point (at which excitation and inhibition are balanced) can vary from 630 nm to 480 nm. Even more variation can be demonstrated if the spatial or temporal properties of the stimulus are altered.

Close to its null point, a given cell will signal a change in wavelength by a reversal in response polarity. Thus the enormous heterogeneity of null points and sensitivity maxima results in a large range of precise wavelength discriminators. Therefore, it is not surprising to find that color discrimination increases with the size of the area stimulated since more (and different kinds of) cells would be

stimulated. However the individual cell is not actually "seeing" color as we generally think of it, but only responding to a narrowed spectral window.

The blue cone system is considered separately because in many respects - anatomy, electrophysiological and psychophysical responses, and possibly genetics - it seems to have more in common with the rods than with the red and green cones.

The blue cones are located perifoveally (Marc and Sperling 1977) and seem to be widely spaced at 10' of arc (Williams et al. 1981). Like the rods, the blue cones appear to utilize only one type of bipolar cell rather than the two types (flat and invaginating) described for the long wavelength system. This might be related to the finding of almost exclusively "ON" center retinal ganglion cells in the blue system (Gouras and Zrenner 1981).

Electrophysiological studies suggest that the blue system response function becomes saturated at low levels of light, that the responses have smaller amplitudes and longer latencies than the red-green system, and that it lacks an "OFF" effect so that it is almost exclusively excited by short wavelength light. The blue cone system seems to have lower spatial and temporal resolution than the red and green cone systems. These properties are expressed in psychophysical testing by the reduced visual acuity and reduced contrast sensitivity (Green 1968), and the higher spatial summation and lower flicker fusion frequency (Brindley 1966) of the blue cone system. Green (1969) speculates that this latter finding might be due to the depressed

modulation sensitivity of the mechanism reflected in its well known high Weber fraction.

The blue cones' widely spaced anatomical distribution, high spatial summation and large receptive fields suggest that they are not involved in the resolution of high spatial frequencies needed for good visual acuity. In addition their consistent action spectra with a constant neutral point at 490 nm suggest the blue cones are somewhat limited in their contribution to the analysis of chromatic information.

With all its limitations one might wonder why we have the blue system at all, particularly with such a well-developed mid-spectral system. However it is the weak points in the red-green system which the blue system appears to compensate for. At its neutral point a cell is unresponsive to light since (by definition) excitation and inhibition cancel each other. Despite their range of responsiveness, the neutral point for most red-green opponent cells occurs near 560 nm to 570 nm. This weakness is compensated for by the blue-long system which has its maximum sensitivity near the neutral point of the red-green system and vice versa. In addition, it appears that the sensation of white (which excites "blue" cells) must depend upon the simultaneous excitation of On-Center red, green and blue cells. Blue cones also contribute to the perception of violet when combined with input from the red cone system. However, it is unclear at what stage the two signals are fed together.

The color vision losses evident in this study might represent an

impairment in the opponent processing system. The generalized loss of wavelength discrimination demonstrated on both the FM 100-Hue test and the anomaloscope might reflect impairment of the "blue" versus "long wavelength" opponent system. The "null" point where the red-green system is most insensitive occurs around 560-570 nm. This is normally compensated for by the "blue-long wavelength" opponency system which is maximally sensitive in this range. Thus a loss or decrement in the blue cone system might cause a generalized wavelength discrimination problem.

Although electrophysiological investigation with microelectrode recordings from retinal ganglion cells in monkeys has provided valuable insight into color opponent mechanisms, different methods must be employed to investigate color opponent processes in human subjects. King-Smith and his associates (King-Smith 1975; King-Smith, Kranda and Wood 1976) have developed a psychophysical technique which requires the observer to detect the presence of a flickering chromatic central field on a strong white background. At rapid rates of temporal alteration (25 Hz), flicker detection spectral sensitivity shows a single maximum at 560 nm and resembles a conventional luminous efficiency function obtained by heterochromatic flicker photometry. At slower temporal frequencies (1 Hz), the flicker detection spectral sensitivity has three maxima: 450 nm, 525 nm and 600 nm. King-Smith suggests that the single-peaked function at the high flicker rate represents achromatic luminance processing (mediated by large diameter fast (Y) cells), and the triple peaks present at the lower flicker rate represent chromatic

signals (mediated by the slow X system) (Zisman, King-Smith and Bharalava 1978). With this technique King-Smith et al. (1976) reported a patient with an unusual acquired color deficit which they attributed to a loss in the opponent system. At a slow flicker rate, rather than the normal three peaked functions, the patient had only a single peak resembling the normal achromatic curve. Assessment of individual spectral sensitivity using chromatic backgrounds failed to reveal any blue cone response. This technique has recently been applied to a group of glaucoma and glaucoma-suspect patients (Adams et al. 1982). In light of our present comparisons between M.S. patients and patients with gluacoma and ocular hypertension, a study of M.S. patients with this same technique might be particularly useful.

It should be noted that the spectral sensitivity maxima for the three peaks obtained in normals with 1 Hz chromatic stimulation on a white background differ somewhat from the peaks obtained using increment detection of chromatic stimuli on a chromatic background developed by Stiles. The Wald-Marre approach, a variation of the Stiles two color threshold technique, utilizes measurement of thresholds for color stimuli under chromatic conditions which are thought to suppress the function of two of the three cone systems. This selective chromatic adaptation provides an opportunity to isolate, represent and measure the three primary color vision mechanisms (CVM's). The spectral sensitivity by this method seems to represent the spectral sensitivity of the individual cone mechanisms more closely than the three "opponent" peaks, obtained by chromatic stimulation

against a white background.

Zrenner (1983) has also utilized a similar increment detection method to assess individual cone spectral sensitivities by appropriate adapting lights: a yellow adapting light to measure blue, a blue-green adapting light to measure red, and a purple (red+blue) adapting light to measure green. Opponent mechanisms were assessed by utilizing a white adapting light. Responses of individual spectral sensitivities and opponency were assessed both psychophysically and with a VEP. In view of the unusual features of the blue cone system (see previous Section) a longer latency, lower amplitude response interval must be adopted to assess the VEP response to 450 nm (blue) light.

Zrenner's work demonstrates the greater sensitivity of the blue system when the other two systems are suppressed with appropriate adapting lights, compared with the reduced sensitivity of the blue system in the presence of a white adapting light. He interprets this as evidence of the inhibitory effect of the long wavelength sensitive cones on the short wavelength system.

2.) Perhaps lesions which produce VEP delays are in the optic nerve whereas lesions which cause "blue" color vision deficits are post chiasmal, possibly in the cerebral hemisphere.

A number of authors regard a delayed response to a transient pattern-reversal VEP as a reliable index of optic nerve plaques or pathology (Halliday, McDonald and Mushin 1977, Celesia 1978). In this study there was a positive statistical correlation between a history of

optic neuritis and a prolonged VEP latency. This is consistent with the findings of other studies (cited above) and supports our diagnosis of optic neuritis. There was not a statistically significant correlation between abnormal VEP responses and 'blue' color vision deficits; nor was there a correlation between optic neuritis and 'blue' color deficits. Since M.S. is a demyelinating disease and myelination (generally) begins posterior to the lamina cribrosa (Lumsden 1970) I would not expect the lesion responsible for the color vision losses to be retinal in origin (i.e. anterior to the optic nerve). It seems more likely the lesions are posterior to the optic nerve. This hypothesis is supported by the work and results of other investigators who have found an acquired blue-yellow defect together with overall loss in chromatic discrimination in patients with cerebral lesions (Birch in Pokorny et al. 1979, p. 318 and 319; Birch-Cox 1976, Meadows 1974).

If some of the chromatic disturbances found in M.S. patients in this study are due to post-chiasmal lesions, one might expect such lesions to produce bilateral color vision defects. This was in fact the case in almost all patients assessed with the anomaloscope. Chromatic discrimination losses determined by anomaloscope testing were present in both eyes in six of seven patients who failed this test. On the FM 100-Hue test there were bilateral color vision disturbances in 10 of 18 patients who had an abnormal total error score.

A number of explanations are possible for the monocular color vision abnormalities which occurred. 1. Monocular color vision abnormalities could be due to optic neuritis. Although I contend that

optic neuritis is not the only cause of color vision disturbances in M.S., the condition could certainly produce some of the color abnormalities detected. 2. Functional deficits have been shown to be exquisitely selective in some M.S. patients, affecting for example sensitivity to spatial frequencies in one range while leaving other spatial frequencies intact (Regan 1980, Bodis-Wollner et al. 1979). Might it be possible for a discrete post-chiasmal lesion in a small group of fibres to affect, for example, only the crossed nasal fibres while sparing the uncrossed temporal fibres, which might produce a contra-lateral monocular color defect. Documentation of such a defect would require a careful visual field examination, ideally using a perimeter equipped with calibrated blue, green and red filters. It is possible that a small lesion such as the hypothetical one described above to account for a monocular color defect, might be more susceptible to variations of the disease (outlined in Section 1.2.3) than the larger lesions hypothesized to cause bilateral color vision deficits. This may account for the more consistent findings in patients with bilateral color vision defects on the FM 100-Hue test. When the FM 100-Hue test was repeated in selected patients as part of the anomaloscope study, patients with bilateral abnormal error scores demonstrated abnormal error scores in both eyes on both occasions. However, patients with a borderline abnormal error score in one eye on the first examination demonstrated a borderline normal score on a subsequent examination.

3.) The lack of a statistically significant correlation between abnormalities in the VEP and 'blue' color vision deficits may occur because color vision and VEP information represent different physiological channels within the visual system. The major difficulty in proving or disproving this hypothesis is the ambiguity which exists in defining a channel. In psychophysical work the term 'channel' or 'mechanism' is used to describe a separate processing unit which is preferentially sensitive to a particular stimulus (Braddick et al. 1978). However the precise neural structures involved in such processing are not defined. Certain channels clearly reflect the interaction of groups of neurons, such as Stile's 'threshold versus radiance' curves which he termed π mechanisms (Pokorny and Smith 1979, pp. 142-145).

Other psychophysically determined channels such as those preferentially sensitive to the spatial frequency or orientiation of a grating pattern (Campbell and Robson 1968, Blakemore and Campbell 1969), seem to have a correlate in the individual cortical neurons which respond preferentially to bars (or gratings) of a particular spatial frequency and orientation (Hubel and Wiesel 1962, Hubel and Wiesel 1968).

There is electrophysiological evidence of two physiological systems for the processing of visual information (Enroth-Cugell and Robson 1966, Lennie 1980, Van Essen 1979, Boycott and Wässle 1974; Rodieck 1979).

1. The fast (Y, phasic, transient, more peripheral, non-opponent)

system is subserved by large neurons with large receptive fields, and large axons with fast conduction velocities. It is preferentially sensitive to low spatial frequencies and is predominantly color-blind.

2. The slow (X, tonic, sustained, mostly central, color opponent) system is subserved mainly by the "midget" system with small receptive fields and small-diameter axons with slow conduction velocities. It is preferentially sensitive to high spatial frequencies and is hue-sensitive.

The fast system appears well suited for detecting movement and signalling the cortex quickly about the presence of something needing to be attended to. Once the fovea is directed to the object of regard the slow system can provide detailed information with its high visual acuity and wavelength discrimination.

These electrophysiological findings appear to have correlates in certain psychophysical results. Tolhurst (1973) demonstrated the existence of two separate psychophysical channels which he speculates might equate with the X and Y type of cells. He suggests that the "movement sensitive" channel which responds to large (low spatial frequency) moving gratings might correlate with the Y system; and the detection of stationary small (high spatial frequency) gratings might correlate with X cells. Kulikowski and Tolhurst (1973) also drew parallels between the pattern-detection and flicker detecting channels described by Keesey and the X and Y systems respectively.

Form versus movement appears to fit well with the X versus Y

dichotomy. The major difficulty is deciding which "channel" analyzes luminance. This dilemma arises partly because of the well described temporal differences in the response to chromatic and achromatic flicker (King-Smith 1975). Pure chromatic flicker in which spectral composition but not luminance changes is most effective at low temporal frequencies (1 c/s). However, pure luminance changes with a constant hue are more effective at high temporal frequencies (25 c/s). Because of these differences, it has been suggested that two functionally or anatomically different pathways (channels or classes of neurons) are responsible for processing chromatic and luminous flicker (King-Smith 1975). The former is presumed to receive antagonistic signals from three spectrally different cone mechanisms (i.e. the X color-opponent tonic cells), whereas the latter may receive synergistic signals from two spectrally different cone mechanisms (i.e. the Y, non-opponent phasic cells) (Boynton 1979, p. 212). Ingling (Ingling and Drum 1973, Ingling 1978), however, favors the proposition that a channel designed to encode and transmit information about hue differences also encodes information about luminance differences because of an antagonistic center versus surround mechanism, i.e. both functions are served by the "X" channel. These hypotheses were tested electrophysiologically (Zrenner 1983) by stimulating a single color opponent cell with the two types of flicker. The same cell responded to chromatic flicker at low frequencies with an antagonistic, phasic response, but responsed to luminous flicker at high frequencies with a synergistic, tonic response. Thus, the color opponent "X" system does seem capable of

processing both chromatic and achromatic flicker.

What is a channel? Is it a discrete neurological entity? If so, then luminance can be handled by the same channel (or cell) as chromatic information. Is it a separate functional unit? If so, then the same cell responding in different ways (tonic for chromatic information and phasic for luminance information) may constitute separate channels for these two functions.

4.) The generalized loss in wavelength discrimination evident on the FM 100-Hue test is caused by reduced 'psychological' discriminative abilities generally, rather than a color vision problem in particular. The main evidence against this hypothesis is the data from the anomaloscope testing. On the anomaloscope, although M.S. patients demonstrated profound losses in wavelength discrimination on the 'blue' equations, discrimination losses were not as great on the red-green equation. In figure 10, the red-green discrimination losses in M.S. patients without optic neuritis are comparable to those which occurred in patients with ocular hypertension, a population in which one might expect normal 'psychological' discrimination.

4.6 CONCLUSIONS

1. Color vision defects were present in a significant number of patients with multiple sclerosis, regardless of whether they had evidence of, or a past history of, optic neuritis.

2. Color vision defects were demonstrable with the first 15 Ishihara plates (45% of patients demonstrated abnormalities). However, disturbances of color vision were brought out more dramatically and reliably with the Farnsworth-Munsell 100-Hue test (50% of patients demonstrated abnormalities). The P-N anomaloscope was the most useful test used in this study (70% of patients demonstrated abnormalities) since it provided the most sensitive, qualitative and quantitative assessment of color vision losses.
3. On the FM 100-Hue test the defects presented as a generalized loss in wavelength discrimination, with increased abnormalities in the "blue" area of the spectrum.
4. Chromatic discrimination on the anomaloscope in M.S. patients with color vision disturbances was always abnormal for the yellow-blue equation (13/13 eyes), usually abnormal for the green-blue equation (10/13 eyes) and abnormal in about half the cases for the red-green equation (7/13 eyes).
5. There was a positive statistical correlation between A) a history or present signs of optic neuritis, B) an abnormal VEP latency and C) a disturbance in the red-green equation on the anomaloscope. This supported our diagnosis of optic neuritis.
6. In M.S. patients there were profound losses in chromatic discrimination on the anomaloscope 'blue' equations, compared with losses which occurred for patients with raised intraocular pressure. These severe losses in 'blue' discrimination were

less affected by a history of optic neuritis than were the losses which were evident on the red-green equation.

7. These findings could be interpreted in the following manner:

   A) Color vision losses might occur in M.S. as a result of lesions located post-chiasmally, independent of optic nerve involvement.

   B) M.S. might affect the opponent processing of chromatic information.

   C) Color vision and VEPs might be handled by different information processing channels within the visual system.

8. The assessment of color vision is a useful option to consider in the clinical evaluation of patients with multiple sclerosis, even if other indicators of visual functions (including visually evoked potentials) are normal.

REFERENCES

Adams, A.J., Atkin, A., Pods, Bodis-Wollner, I. "Abnormalities of the visual system in ocular hypertension and glaucoma", Proceedings of the International Perimetric Society, Sacramento, 1982.

Adams, A.J., Rodic, R., Husted, R., Stumper, R. "Spectral sensitivity and color discrimination changes in glaucoma and glaucoma-suspect patients", Invest. Ophthal. Vis. Sci., 23:516-524, 1982.

Alpern, M., Mindel, T., Torii. "Are there two types of deuteranopes", J. Physiol., 199:443-456, 1968.

Anderson, D.R. "Pathology of the glaucomas", Brit. J. Ophthal., 56:146-156, 1972.

Anderson, D.R. "Pathogenesis of glaucomatous cupping: a new hypothesis", in Symposium on Glaucoma, Transactions of the New Orleans Academy of Ophthalmology. Saint Louis: C.V. Mosby Company, 1975, pp. 81-90.

Aspinall, P.A. "Inter-eye comparison on the 100-Hue test", Acta Ophthal., 52:307-316, 1974.

Asselman, P., Chadwick, D.W., Marsden, C.D. "Visual evoked responses in the diagnosis and management of patients suspected of multiple sclerosis", Brain, 98:261-282, 1975.

Birch, J. "Acquired color defects of central origin", in Pokorny, J., Smith, V.C., Verriest, G., Pinckers, A.J.L.G.. (eds.), Congenital and acquired Color Vision Defects. New york: Grune and Stratton, 1979, pp. 318-321.

Birch-Cox, J. "Design of diagnositic tests for congenital and acquired color vision defects", Mod. Prob. Ophthal., 17:196-201, 1976.

Blakemore, C., Campbell, F.W. "On the existence of neurons in the human visual system selectively sensitive to the orientation and size of retinal images", J. Physiol., 203:-237-260, 1969.

Bodis-Wollner, I., Hendley, C.D., Atkin, A. "Evaluation by evoked potentials of dissociated visual functions in patients with cerebral lesions", in Desmedt, J.E. (ed.), Visual Evoked Potentials in Man: New Developments. Oxford: Clarendon Press, 1977, pp. 514-524.

Bodis-Wollner, I., Hendley, C.D., Mylin, L.H., Thornton, J. "Visual evoked potentials and the visogram in multiple sclerosis", Ann. Neurol., 5:40-47, 1979.

Bowmaker, J.K, Dartnall, H.J.A. "Visual pigments of rods and cones in a human retina", J. Physiol., 298:501-511, 1980.

Boycott, B.B, Wässle, H. "The morphological types of ganglion cells of the domestic cat's retina", J. Physiol., 240:397-419, 1974.

Boynton, R.M. Human Color Vision. New York: Holt, Rinehart and Winston, 1979.

Braddick, O., Campbell, F.W., Atkinson, J. "Channels in vision: basic aspects", in Held, R., Leibowitz, H.W., Teuber, H-L. (eds.), Handbook of Sensory Physiology: Perception, Vol. VIII. Berlin: Springer-Verlag, 1978, pp. 3-8.

Brindlei, G.S. Physiology of the Retina and Visual Patterns (ed. 2). Baltimore: Williams and Wilkins, 1970.

Campbell, F.W., Robson, J.G. "Application of fourier analysis to the visibility of gratings", J. Physiol., 197:551-566, 1968.

Celesia, G.G. "Visual evoked potentials in neurological disorders", Am. J. EEG Technol., 18:47-59, 1978.

Chiappa, K.H. "Pattern shift visual, brainstem auditory, and short latency somatosensory evoked potentials in multiple sclerosis", Neurology, 30(2):110-123, 1980.

Cook, S.D., Dowling, P.C., Russell, W.C. "Neutralizing antibodies to canine distemper and measles virus in multiple sclerosis", J. Neurol. Sci., 41:61-70, 1979.

Cook, S.C., Dowling, P.C., "Multiple sclerosis and viruses: An overview", Neurology, 30(2):80-91, 1980.

Cox, J. "Color vision defects acquired in diseases of the eye",
a) Br. J. Physiol. Opt., 17:195-216, 1960;
b) Br. J. Physiol. Opt., 18:3-32, 1961a;
c) Br. J. Physiol. Opt., 18:67-84, 1961b.

de Monasterio, F.M. "Functional properties and presumed roles of retinal ganglion cells of the monkey", in Szentógothai, J., Hámuri, J., and Palkovits, M. (eds.), Adv. Physio. Sci., Vol. 2. Regulatory Functions of the CNS Subsystems. 28th International Congress of Physiological Sciences, Budapest: Pergamon Press, 1981, pp. 261-268.

Drance, S.M. "The glaucomatous visual field", Brit. J. Ophthal., 56:186-200, 1972.

Duke-Elder, Sir S., Jay, B. "Glaucoma and hypotony, Section III", in Duke-Elder, Sir S. (ed.), System of Ophthalmology, Vol. XI. St. Louis: C.V. Mosby Co., 1969, pp. 379.

Ellison, G.W., Myers, L.W. "Immunosuppressive drugs in multiple sclerosis", Neurology, 30(2):28-32, 1980.

Enroth-Cugell, C., Robson, J.G. "The contrast sensitivity of retinal ganglion cells of the cat", J. Physiol., 187:517-552, 1966.

Farnsworth, D. The Farnsworth-Munsell 100-Hue Test Manual (revised ed.). Baltimore: Munsell Color Compny, 1957.

Francois, J., Verriest, G. "On acquired deficiency of colour vision, with special reference to its detection and classification by means of the tests of Farnsworth", Vision Res., 1:201-219, 1961.

Funk, Wagnall, New Comprehensive International Dictionary of the English Language, Encyclopedia edition. Chicago: JG Ferguson Publishing Company, 1977.

Galvin, R., Regan, D. and Heron, J.R. "Impaired temporal resolution of vision after acute retrobulbar neuritis", Brain, 99:255-268, 1976.

Gartner, S. "Optic neuropathy in multiple sclerosis", Arch. Ophthal., 50:718-726, 1953.

Gouras and Zrenner, "Color vision: a review from a neurophysiological perspective", Progress in Sensory Physiology, 1:139-179, 1981.

Green, D.G. "Sinusoidal flicker characteristics of the color sensitive mechanisms of the eye", Vision Res., 9:591-601, 1969.

Green, D.G. "The contrast sensitivity of the colour mechanisms of the human eye", J. Physiol., 196:415-429, 1968.

Griffin, J.F., Wray, S.H. "Acquired color vision defects in retrobulbar neuritis", Am. J. Ophthal., 86:193-201, 1978.

Halliday, A.M., McDonald, W.I., Mushin, J. "Delayed visual evoked response in optic neuritis", Lancet, 1:982-985, 1972.

Halliday, A.M., McDonald, W.I., Mushin, J. "Visually evoked potentials in patients with demyelinating disease", in Desmedt, T.E. (ed.), Visually Evoked Potentials in Man: New Developments. Oxford: Clarendon Press, 1977, pp. 438-449.

Harter, M.R. "Evoked cortical responses to checker board patterns: effects of check size as a function of retinal eccentricity", Vision Res., 10:1365-1376, 1970.

Harter, M.R., White, C.T. "Effects of contour sharpness and check size on visually evoked cortical potentials", Vision Res., 8:701-711, 1968.

Heron, J.R., Regan, D. and Milner, B.A. "Delay in visual perception in unilateral optic atrophy after retrobulbar neuritis", Brain, 97:83-92, 1974.

Hubel, D.H. and Wiesel, T.W. "Receptive fields and functional architecture of monkey striate cortex", J. Physiol. (Lond.), 195:215-225, 1968.

Hubel, D.H., Wiesel, T.W. "Receptive fields, binocular interaction and functional architecture in the cat visual cortex", J. Physiol., 160:106-154, 1962.

Hurvich, L.M. Color Vision. Sunderland: Sinauer Associates Inc., 1981.

Ingling, C.R. "Luminance and opponent color contributions to visual detection and to temporal and spatial integration: Comment", J. Opt. Soc. Am., 68(8):1143-1146, 1978.

Ingling, C.R. and Drum, B.A. "Retinal receptive fields: Correlations between psychophysics and electrophysiology", Vision Res., 13:1151-1163, 1973.

Jung, R. "Visual perception and neurophysiology", in Jung, R. (ed.), Handbook of Sensory Physiology, Vol. VII/3: Central processing of visual information, Part A. Berlin: Springer-Verlag, 1973, pp. 3-8, 118-120.

King-Smith, P.E. "Visual detection analysed in terms of luminance and chromatic signals", Nature, 255:69-70, 1975.

King-Smith, P.E. and Carden, D. "Luminance and opponent color contribution to visual detection and to temporal and spatial integration: Authors' reply to comments", J. Opt. Soc. Am., 68(8):1146-1147, 1978.

King-Smith, P.E., Kranda, K., Wood, I.C.J. "An acquired color defect of the oppnent-color system", Invest. Ophthal., 15:584-587, 1976.

Kinnear, P.R. "Proposals for scoring and assessing the 100-Hue test", Vision Res., 10:423-433, 1970.

Kirkham, T.H., Coupland, S.G. "Multiple regression analysis of diagnostic predictors in optic nerve disease", Can. J. Neuro. Sci., 8:67-72, 1981.

Krill, A.E., Fishman, G.A. "Acquired color vision defects", Trans. Am. Acad. Ophthal. Otoloryngol, 75:1095-1112, 1971.

Kulikowski, J.J., Tolhurst, D.J. "Psychophysical evidence for sustained and transient detectors in human vision", J. Physiol., 232:149-162, 1973.

Kurtzke, J.F. "Further notes on disability evaluation in multiple sclerosis, with scale modifications", Neurology, 15:654-661, 1965.

Kurtzke, F.J. "Epidemiologic contributions to multiple sclerosis: An overview", Neurology, 30(2):61-79, 1980.

Lakowski. R. "Is the deterioration of color discrimination with age due to lens or retinal changes", Die Farbe, 11:69-86, 1962.

Lakowski, R. "A critical evaluation of color vision tests", Brit. J. Physiol. Opt., 23:186-209, 1966.

Lakowski, R. "Theory and practise of color vision testing. A review", Part 1. Br. J. Indus. Med., 26:173-189, 1969(a);
Part 2. Br. J. Indus. Med., 26:265-288, 1969(b).

Lakowski, R. "Calibration, validation and population norms for the Pickford-Nicolson anomaloscope", Br. J. Physiol. Opt., 26: 166-182, 1971.

Lakowski, R., Bryett, J., Drance, S.M. "A study of color vision in ocular hypertensives", Can. J. Ophthal., 7:86-95, 1975.

Lakowski, R., Drance, S.M. "Acquired dyschromatopsias: the earliest functional losses in glaucoma," Doc. Ophthal., 19: 159-165, 1979.

Lakowski, R., Oliver, K. "Effect of pupil diameter on color vision test performance", Mod. Prob. Ophthal., 13:307-311, 1974.

Lanthony, P. "The desaturated Panel D-15", Doc. Ophthal., 46: 185-189, 1978a.

Lanthony, P. "The new color test", Doc. Ophthal., 46:191-199, 1978b.

Lennie, P. "Parallel visual pathways: A review", Vision Res., 220:561-594, 1980.

Linksz, A. "The clinical characteristics of acquired color-vision defects", in Straatsma, B.R., Hall, M.O., Allen, R.A. (eds.), The Retina: Morphology, Function and Clinical Characteristics. Berkeley University: California Press, 1969, pp. 583-592.

Lisak, R.P. "Multiple sclerosis: Evidence for immunopathogenesis", Neurology, 30(2):99-105, 1980.

Lumsden, C.E., in Vinken, P.J., Bruyn, G.W. (eds.), Handbook of Clinical Neurology, Vol. 9: Multiple Sclerosis and Other Demyelination Diseases. Amsterdam: North Holland Publishing Company, 1970, pp. 234-237, 305-308.

Marc, R.E. and Sperling, H.G. "Chromatic organization of primate cones", Science, 196:454-456, 1977.

McAlpine, D., Lumsden, L. Acheson, D. Multiple Sclerosis: A Reappraisal. Edinburgh: E & S Livingstone Ltd., 1965.

McDonald, W.I. "Pathophysiology of conduction in central nerve fibres", in Desmedt, J.E. (ed.), Visual Evoked Potentials in Man: New Developments. Oxford: Clarendon Press, 1977, pp. 427-437.

McDonald, W.I., Halliday, A.M. "Diagnosis and classification of multiple sclerosis", Br. Med. Bull., 33:4-8, 1977.

McKhann, G.M. "Multiple Sclerosis", Ann. Rev. Neurosci., 5:219-239, 1982.

Meadows, J.C. "Disturbed perception of colors associated with localized cerebral lesions", Brain, 97:615-632, 1974.

Mollon, J.D. "Color Vision", Ann. Rev. Psychol., 33:41-85, 1982.

Parker, J.A. "Farnsworth 100-Hue scoring for acquired color vision deficiency by weighted functions", Comp. in Ophthal., 97-99, 1979.

Pickford, R.W., Lakowski, R. "The Pickford-Nicolson anomaloscope", Br. J. Physiol. Opt., 17:131-150, 1960.

Pokorny, J., Smith, V.C., Verriest, G. and Pinckers, A.J.L.G. (eds.) Congenital and Acquired Color Vision Defects. New York: Grune and Stratton, 1979.

Pokorny, J., Smith, V.C. and Verriest, G. "Physiological and theoretical bases of normal color vision", in Pokorny, J., Smith, V.C., Verriest, G. and Pinckers, A.J.L.G. (eds.), Congential and Acquired Color Vision Defects. New York: Grune and Stratton, 1979.

Poser, C.M., "The myelinoclastic diseases", in Merritt, H.H. (ed.), A Textbook of Neurology. Philadelphia: Lea and Febiger, 1979, pp. 768-779.

Prineas, J.W. and Connell, F. "Remyelination in multiple sclerosis", Ann. Neurol., 5:22-31, 1978.

Quigley, H.A., Addick, E.M., Green, W.R. "Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage", Arch. Ophthal., 99:635, 1981.

Regan, D.M. "New visual tests in multiple sclerosis", in Thompson, H.S. (ed.), Topics in Neuro-Ophthalmology. Baltimore: Williams and Wilkins, 1980, pp. 219-242.

Regan, D.M., Milner, B.A., Heron, T.J. "Delayed visual perception and delayed visually evoked potentials in the spinal form of multiple sclerosis and in retrobulbar neuritis", Brain, 99:43-66, 1976.

Regan, D.M., Silver, R., Murray, T.J. "Visual acuity and contrast sensitivity in multiple sclerosis - hidden visual loss", Brain, 100:563-579, 1977.

Regan, D.M., Whitlock, J.A., Beverley, K.F. "Orientation specific losses of contrast sensitivity in multiple sclerosis", Invest. Ophthal., 19:324-328, 1980.

Riggs, L.A., Wooten, B.R. "Electrical measures and psychophysical data on human vision", in Jameson, D., Hurvich, L.M., (eds.), Handbook of Sensory Physiology, Vol. VII/4: Visual Psychophysics. Berlin: Springer-Verlag, 1972, pp. 723-725.

Rigolet, M.H., Mallecourt, J., Leblanc, M., Chain, F. "Etude de la vision des couleurs et des potentiels evoques visuels dans le diagnostic de la sclerose en plaques", J. Fr. Ophthalmoi., 10(2): 553-560, 1979.

Rodieck, R.W., "Visual pathways", Ann. Rev. Neurosi., 2:193-225, 1979.

Rushton, W.A.H. "Visual pigments in man", in Dartwall, H.J.A. (ed.), Handbook of Sensory Phsiology, Vol. VII/1. Berlin: Springer-Verlog, 1972, pp. 364-394.

Schauf, C.L., Peneck, T.L., Davis, F.A., Rooney, M.W. "Physiologic basis for neuroelectric blocking activity in multiple sclerosis", Neurology, 31:1338-1341, 1981.

Taylor, W.O.G. "Problems in performance and interpretation of Farnsworth's 100-Hue test", Mod. Prob. Ophthal., 13:73-78, 1974.

Titcombe, A.F. and Willison, R.G. "Flicker fusion in multiple sclerosis", J. Neurol. Neurosurg., Psychiatry, 24:260-265, 1961.

Tolhurst, D.J., "Separate channels for the analysis of the shape and the movement of a moving visual stimulus", J. Physiol., 231: 385-402, 1973.

Van Essen, D.C. "Visual areas of the mammalian cerebral cortex", Ann. Rev. Neurosci., 2:227-263, 1979.

Verriest, G. "Further studies on acquired deficiency of color discrimination", J. Opt. Soc. Am., 53:185-195, 1963.

Vos, J.J., Walraven, P.L. "On the derivation of the foveal receptor primaries", Vision Res., 11:799-818, 1970.

Wald, G. "The receptors of human color vision", Science, 145: 1007-1017, 1964.

Wald, G. "Defective Color Vision and Its Inheritance", Proc. Natl. Acad. Sci. USA, 55:1347-1363, 1966.

Wildberger, H.G.H, van Lith, G.H.M. "Color vision and visually evoked response (VECP) in the recovery period of optic neuritis", Mod. Prob. Ophthal., 17:320-324, 1976.

Williams, D.R., Macleod, D.I.A., Hayboe, M.M. "Punctate sensitivity of the blue-sensitive mechanism", Vision Res., 21: 1357-1375, 1981.

Zisman, F., King-Smith, P.E., Bhargava, S.K. "Spectral sensitivities of acquired color defects analysed in terms of color opponent theory", Mod. Prob. Ophthal., 19:254-257, 1978.

Zrenner, E. Neurolphysiological Aspects of Color Vision in Primates. Berlin: Springer-Verlag, 1983.

APPENDIX

Aquisition Survey

American Optical Hardy Rand Rittler Plates (AO-HRR)	no longer available
City University Plates	available in North America from Imperial Optical Company Keeler Instruments, Ltd. 21-29 Marylebone Lane London WIM 6DS Tel.: 01-935-8512
Ishihara Plates	AOCO Limited P.O. Box 5500, 161 Bridge St. W. Belleville, Ontario M8N 5C6
Farnsworth Munsell 100-Hue Test (FM 100-Hue)	Munsell Color, Macbeth Division 2441 North Calvert Street Baltimore, Maryland 21218
Farnsworth Dichotomous Test (Panel D-15)	Munsell Color, Macbeth Division 2441 North Calvert Street Baltimore, Maryland 21218
Macbeth Daylight Lamp	Macbeth Koll Morgan Corp. P.O. Box 950 Newburgh, New York 12550
Verilux Daylight Bulbs	Verilux Greenwich, Conn. (203) 869-3750

Table A.1 CRITERIA FOR THE CLASSIFICATION OF CASES OF MULTIPLE SCLEROSIS

CLASSIFICATION	CRITERIA	NOTES
PROVED	Diagnosis established at necropsy	
CLINICALLY DEFINITE	Remitting and relapsing history with two or more episodes	A relapse is reckoned as a period of at least 24 hrs.in which there is worsening of an existing symptom or group of symptoms, provided that the course has been stationary or has improved during the previous month(Schumacher et al 1965).
	AND	
	Evidence of lesions at two or necessarily separate sites in the central nervous system(CNS).	Bilateral optic nerve lesions are counted as a single lesion only.
	AND	
	Lesions predominately in the white matter	
	AND	
	Age of onset of symptoms 10-50 years.	
	AND	
	History of signs or symptoms for one year or longer	Cases of shorter duration otherwise fulfilling these criteria are classed as "early probable"
	AND	
	No better explanation for the observed abnormalities	
EARLY PROBABLE OR LATENT.	Single episode suggestive of MS	
	AND	
	Evidence of lesions at two or more necessarily separate sites in the CNS.	Cases suggestive of acute disseminated encephalomtelitis and transverse myelitis are excluded
	OR	
	Remitting or relapsing course	
	AND	
	Evidence of only one lesion associated with MS.	
PROGRESSIVE PROBABLE	Progressive history of paraplegia	
	AND	
	Evidence of lesions at two or more necessarily separate sites in the CNS	
	AND	
	Other causes excluded	
PROGRESSIVE POSSIBLE	Progressive history of paraplegia	
	AND	
	Evidence of only one lesion	
	AND	
	Other causes excluded	
SUSPECTED	Single episode suggestive of MS without evidence of any lesion or with evidence of a single lesion only	
	OR	
	Recurrent optic neuritis(unilateral or bilateral) with one additional episode not involving the optic nerve but without evidence of lesions outside the eye	Recurrent optic neuritis without other features is excluded

Table A.2 Ishihara Plates: Evalation of Possible Criteria for Differentiating Patients from Controls*

Candidate Criteria	Failure Rate			
	Controls		Patients	
	Eyes/54	Subjects/27	Eyes/80	Subjects/40
1. Fail = 1 or more errors per 24 plates. (Pass = no errors per 24 plates.)	38(70%)	20(74%)	70(87.5%)	39(97.5%)
2. Fail = 3 or more errors per 24 plates. (Pass = 2 or fewer errors per 24 plates.)	22(41%)	13(48%)	39(49.0%)	23(57.5%)
3. Fail =4 or more errors per 24 plates. (Pass = 3 or fewer errors per 24 plates.)	16(30%)	10(37%)	31(39.0%)	19(47.5%)
4. Fail = 3 or more errors on first 17 plates. (Pass = 2 or fewer errors on first 17 plates.)	5(9%)	3(11%)	18(22.5%)	14(35.0%)
5. Fail = 2 or more errors on first 16 or 15 plates. (Pass = 1 or fewer errors on first 16 or 15 plates.)	5(9%)	3(11%)	25(31.0%)	18(45.0%)
6. Fail = 1 or more errors on first 16 or 15 plates. (Pass = no errors on first 15 or 16 plates.)	24(44%)	16(59%)	51(64.0%)	29(72.5%)

* Category 5 appears the most satisfcatory.

Table A.3 Farnsworth-Munsell 100-Hue Test: Norms (Background Data for Table A.4) Comparison of Standards for Age-Related Performance on the FM 100-Hue Test

	Verriest Population (1963)			Calgary Population (this study)		
		100-Hue Test Score			100-Hue Test Score	
Age	N(Subjects)	Mean	S.D.	N(Eyes)	Mean	S.D.
20-24	94	36.3	31.2	8	34.5	15.2
25-29	51	47.4	29.4	8*	45.6*	60.8*
				6†	13.7†	13.2†
30-34	33	54.7	35.2	14	43.4	36.3
35-39	37	56.8	34.2	8	26.1	12.6
40-44	32	62.4	28.5	6*	97.5*	90.3*
				4†	40.6†	24.8†
45-49	30	90.4	39.3	4	51.0	26.4
50-54	38	71.5	31.3	4	62.5	9.0
55-59	31	96.7	41.9	2	43.0	32.5

* including "abnormal control"
† excluding "abnormal control"

Table A.4 Farnsworth-Munsell 100-Hue Test: Norms for Comparison of Standards for Age Related Performance on the FM 100-Hue Test in Normal Populations*

	Verriest Population (1963)		Calgary Population (this study)	
Age	Maximum Score Observed in 95% of Population	2 S.D. Above Mean	2 S.D. Above Mean	3 S.D. Above Mean
20-24	74	98.7	64.9	80.1
25-29	92	106.2	167.2† 40.1§	228.0† 53.3§
30-34	106	125.1	116.0	152.3
35-39	120	125.2	51.3	63.9
40-44	134	119.4	278.1† 90.2§	368.4† 115.0§
45-49	144	169.0	103.8	130.2
50-54	154	134.1	80.5	89.5
55-56	164	180.5	108.0	140.5

* higher than above number = abnormal score or failure of test
† including "abnormal control"
§ excluding "abnormal control"

Table A.5 Farnsworth-Munsell 100-Hue Test: Interocular Differences - Possible Criteria for Establishing Abnormal Interocular Differences

Number of 'Failures'	Maximum Difference for 95% of Control Group* Difference = 45	2 S.D. Above Mean Difference = 41	3 S.D. Above Mean Difference = 55	$\overline{R} - \overline{L} > 3.0$
Control Group N = 27 Subjects				
Abnormal Total Error Score	2 (7.4%)	2 (7.4%)	2 (7.4%)	2 (7.4%)
Abnormal Interocular Difference	1 (3.7%)	2 (7.4%)	0 (0.0%)	2 (7.4%)
Total Number of Failures	3 (11.1%)	4 (14.8%)	2 (7.4%)	4 (14.8%)
Patient Group N = 40 Subjects				
Abnormal Total Error Score	17 (42.5%)	17 (42.5%)	17 (42.5%)	17 (42.5%)
Abnormal Interocular Difference	3 (7.5%)	4 (10.0%)	1 (2.5%)	2 (5.0%)
Total Number of Failures	20 (50.5%)	21 (52.5%)	18 (45.0%)	19 (47.5%)

* Control Group Mean = 13; Standard Deviation = 14

Table A.6 Farnsworth-Munsell 100-Hue: M.S. Patients with Abnormal Error Scores, Spectral Location of Deficits

Patient	Age	Eye	Optic Neuritis	F.M. Score	Visual Axis (mid point CAP #)	Computer Axis
B.C.	22	R	yes	222	General slight tetartan axis (80+36)	same
		L	yes	304	Semicircle (13-37) Atypical B-Y mono. (42)	similar
T.H.	24	R	yes	106	General slight tritan mono. (45)	different (deutan)
E.R.	26	R	yes	181	Semicircle tritan mono. (46)	same
		L	no	187	Slight scotopic axis (10+55)	same
J.D.	26	R	no	135	General slight tetartan axis (37+79)	same
		L	no	94	General atypical B-Y axis (32+73)	similar
P.R.	26	R	no	99	Slight atypical deutan axis (14+57)	same
		L	no	98	General slight scotopic mono. (30+53)	similar
M.S.	28	R	no	145	Slight scotopic axis (11+55) Slight tetartan (37+73)	similar
		L	yes	147	Tetartan axis (37+78)	same
F.W.	28	R	yes	165	Slight deutan mono. (16) Slight tetartan mono. (34)	similar
L.K.*	30	L	yes	104	Protan axis (20+64) Tritan mono. (47)	different (deutan)
M.M.	31	R	no	114	Atypical B-Y axis (42+77)	similar
P.M.	32	L	yes	107	General	similar
L.S.	33	R	no	194	General slight tetartan axis (36+49) Atypical deutan axs (15+57)	same
		L	yes	152	Tetartan mono. (39)	
D.N.	35	R	no	129	Deutan mono. (59)	similar
		L	no	134	General	different (deutan)
M.S.	36	R	yes	218	Slight tetartan axis (37+76) Tritan mono. (48)	similar
		L	no	133	Tetartan axis (80+35) Deutan axis (18+58)	different (scotopic)
C.G.	37	L	no	121	General slight tetartan (36+80) Slight scotopic (10+56)	similar
B.C.	37	R	yes	227	General	same
		L	yes	191	General slight scotopic mono. (52)	same
S.C.	39	R	yes	138	One misplaced cap	different (tetartan)
G.R.	44	R	yes	178	Scotopic axis (13+54) Atypical B. mono. (43)	similar
		L	yes	184	No conventional axis (70)	different (tetartan)
B.B.*	47	R	no	114	Slight protan mono. (14)	similar
R.B.*	48	L	no	118	Slight deutan mono. (57)	similar
W.A.*	52	L	yes	163	General	similar

* Abnormal interocular difference
Mono. = Monopolar "bulge" of errors.

Table A.7 The Pickford-Nicolson Anomaloscope: Patient Data for Anomaloscope Findings in M.S. Patients with Stable Optic Neuritis

Patient	Age	Eye	VEP	Optic Neuritis	P-N Anomascope								
					Red-Green			Blue-Yellow			Blue-Green		
					MR	MMP	DIAG	MR	MMP	DIAG	MR	MMP	DIAG
E.R.[1]	27	R	abn	yes	ext	N	mild	ext	ext	ext	ext	N	mild
		L	N	no	N±	N	N	ext	ext	ext	ext	N	mild
F.P.	27	R	abn	no			N			N			N
		L	abn	yes			N			N			N
M.S.	28	R	abn	no			N	ext	N	mild	mild	N	mild
		L	abn	yes	ext	ext	ext	ext	N	mild	ext	N	mild
D.L.	29	R	N	yes			N	ext	N	mild	N±	N	N
		L	N	no			N	ext	N	mild	N±	N	N
M.M.	32	R	N	no			N			N			N
		L	abn	yes			N			N			N
M.B.	31	R	N	yes	N±	N	N	ext	N	mild			N
		L	N	no	N±	N	N	ext	N	mild	ext	N	mild
C.G.	38	R	abn	no			N	N±	N±	N±			N
		L	abn	yes	ext	N	mild	ext	ext	ext	ext	N	mild
S.C.[1]	39	R	abn	no	ext	ext	ext	ext	ext	ext	dic	ext	ext
		L	abn	yes	ext	N	ext	dic	ext	dic	dic	ext	dic
H.B.	42	R	abn	yes	N±	N±	N	N	N	N	N	N±	N
		L	N	no			N			N			N

N = normal; mild = mild abnormalities; ext = extensive abnormalities;
dic = dichotomous (very severe abnormalities).
MR = matching range; MMP = mid-matching point; DIAG = diagnosis of color mixing ability.
1 = Extremely abnormal brightness response, 'recruitment phenomenon'