THE EVALUATION OF MULTIPLE SCLEROSIS THROUGH STATIC CHROMATIC PERIMETRY

by

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Abstract

The purpose of the present study was to examine whether or not luminance thresholds through static, chromatic perimetry could be used to distinguish visual threshold losses in multiple sclerosis from that of normal functioning. It was proposed that threshold losses would be greater at both the fovea and near foveal eccentricities due to the assumption that the cone system, unlike the rods, would be the most effected by MS.

Twenty-two MS patients and thirty age matched normals were tested on an extensively modified version of the Fieldmaster F225 Automatic Perimeter. Thresholds were established for an achromatic, red, and blue stimulus along a 195 - 15 degree meridian. Testing was done using a 45 apostilb background, to which the subjects were preadapted prior to testing.

Results indicated that there was extensive cone involvement (loss in chromatic thresholds) for the MS subjects. Significant differences existed at the fovea between normal and clinically definite subjects but not between normal and probable. Correlational analyses indicated great functional changes in retinal
sensitivity for the MS patients. Similar results were obtained between MS patients with and without optic neuritis.

Discriminant analyses indicated that the red filter could correctly classify 86.27% of the normals and MS patients with few false positives or negatives. Log threshold difference values between the fovea and 30 degree nasal eccentricity were used to determine a threshold value which could separate normal profiles from MS profiles.

The typical "swiss cheese" defects reported in the clinical literature were found only for the achromatic and blue filters. No irregular profiles were found for the red filter.

A possible theoretical model based on the results was discussed. Limitations of the study as well as possible future research were also discussed.
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Multiple sclerosis has presented both researchers and clinicians with enormous problems in detecting early onset as well as in understanding the course(s) of the disease. Treatment at present is symptomatic. Despite its identification over 100 years ago, the protean manner in which multiple sclerosis may present itself has made it difficult to develop an accurate clinical description of its features; and, therefore, created difficulty in conducting research such as on the epidemiology of the disease.

Symptomatically, the patient may exhibit motor impairment as well as losses in one or more sensory modalities. Both motor and sensory impairment may appear alone or in some combination. In addition, the severity and progression of the 'disease' is so variable that one may actually have several clinical diseases that are too difficult to differentiate - an argument seen in schizophrenia.

One prominent area of involvement in MS appears to be that of the sensory system, especially the visual. Non-invasive procedures for diagnosing the disease rely upon the detection of abnormalities in the sensory system of interest.

A major assessment procedure, apart from postmortem examination or clinical procedures such as electrophoresis,
is the visual evoked potential. Abnormalities in the visual system due to MS tend to appear in the evoked potential as a reduction in amplitude or greater latency.

Although other methods are currently being studied for assessing visual involvement, it is the writer's belief that they provide ambiguous results. The purpose of the following literature review is to demonstrate that the visual function tests currently employed tend to ignore or confuse the specific contributions of the macula and peripheral retina in revealing MS related functional losses. Both the macula and peripheral retina are affected in MS, with cone functioning possibly being affected the earliest and more severely than the rods. Because of the apparent sensitivity of the optic nerve to demyelination, it is proposed that by examining retinal functioning through chromatic perimetry one may understand the effects of demyelination on the visual system (retina) as well as possibly provide a method for assessing both the presence and severity of MS.

1. MULTIPLE SCLEROSIS

Multiple sclerosis is a remissively progressive disease characterized by the presence of plaques in the central nervous system. It is multi-focal in nature and appears to affect, or at least be symptomatic in males and females between the ages of 10 and 50, with females being affected
1.7:1 times more than males. Prevalence rates for multiple sclerosis are higher in the northern latitudes and comparably rare in Asiatic countries. The risk for contracting multiple sclerosis is said to be four times greater for those living in metropolitan centres than small towns, higher for professional or managerial groups than unskilled workers, higher for caucasians than negroids, fifteen to twenty times greater for first degree relatives of multiple sclerosis victims. Multiple sclerosis is also more likely to be manifested in individuals with a history of infectious diseases. Apart from infections, some of the myriad of factors felt to either precipitate or aggravate multiple sclerosis have been trauma, pregnancy, emotional stress, vaccination and/or innoculation, menstruation, temperature changes, and fatigue. Aetiology of the disease has, at one time or another, been ascribed to a latent virus which may or may not lead to an anti-immunal myelin response, to the presence of histocompatibility antigens (HLA) [related to four loci on chromosome number six] as well as diet (saturated fats) and climate.

A. SYMPTOMATOLOGY

The first account of multiple sclerosis (MS) appears to be that of Augustus d'Este' (1830) who prepared a dissertation on the progression of the disease in himself, preceding the
personal insights provided by Lumsden (1970) some one hundred years. Although Carswell in 1838 and Cruveilhier (1835-1842) are attributed with demonstrating the presence of lesions in the central nervous system, it is Charcot (1868) who is generally accredited with the first clinical description of the syndrome known as MS or disseminated sclerosis (Field, 1977).

Charcot felt that MS did not occur prior to the age of fourteen and after fifty - a belief still held today despite evidence to the contrary (eg. Friedman & Davison, 1945; Elian, 1977; Field, Sinclair & Swank, 1980; Bejar, Dewey & Ziegler, 1984). His description of the cyclical (remission-progression) nature of the symptoms, the presence of plaques in relation to either sensory and/or motor disturbances as well as the problematic presence of silent cases (asymptomatic) is so complete that many feel that very little has been added since. (Field, 1977).

Of particular importance are those diagnostic signs typically referred to as Charcot's Triad of Multiple Sclerosis (Figure 1) (Newell, 1978). According to Charcot, MS is characterized by the presence of nystagmus, optic atrophy (optic neuritis) and scanning speech (slow, pressured speech). The importance of this triad lies in the fact that the majority of its symptoms involve the visual system, indicating, as indeed is the case, that the visual system appears to be highly sensitive to the demyelinating effects of MS.
FIGURE 1

CHARCOT'S TRIAD OF
MULTIPLE SCLEROSIS
Multiple sclerosis is believed to be the result of central nerve fiber demyelination (Lumsden, 1970; McAlpine, Lumsden & Acheson, 1972) as well as possible vascular changes in regions such as the retina (Lumsden, 1970; Bervoets & De Lact, 1984), loss of oligodendrogliocytes and increase in fibrous astrocytes (McDonald, 1974).

Through unknown mechanisms, possibly by immunal responses to viruses wherein lymphocytes and macrophages invade the brain and attack the myelin, the myelin sheath surrounding the axon of a central nerve fibre swells and fragments (Lumsden, 1970; McDonald, 1974). The destroyed sheath is replaced by a sclerotic plaque, a scar resulting from the proliferation of glial cells around the axon (Lumsden, 1970). It is thought that symptoms characteristic of MS are the result of an inability of such plaques to conduct impulses along the axon.

---

1 Myelin, first discovered by Leeuwenhoek in 1717, consists of a plasma membrane deposited by Schwann cells (Figure 2). The myelin sheath is the result of a membrane of the Schwann cell first forming a "flattened sheet" that envelops the axon. The Schwann cell then rotates around the axon until several layers of a conductive lipid known as sphingomyelin is deposited. It is this lipid that increases the resistance to ion flow almost 5,000 fold and decreases capacitance by 1,000 fold (Guyton, 1981). An unmyelinated area between the junction of two adjacent Schwann cells where ions may flow easily between the extracellular fluid and the axon is known as the node of Ranvier. The function of such nodes is to allow saltatory conduction wherein a neuronal signal jumps along a fiber. Although the nodes of Ranvier are unmyelinated, they are covered with a conductive membrane that surrounds the axon underneath the myelin. The function of this nodal (high potassium channels) and internodal (high sodium channels) axon membrane is presently unclear, but is felt to play a major role in specifying which areas of the axon will become myelinated (Waxman & Foster, 1980).
FIGURE 2

FORMATION OF MYELIN SHEATH IN THE PERIPHERAL NERVOUS SYSTEM.
MODIFIED FROM GUYTON (1981, p.116)
After a period of time, slow conduction within demyelinated neurons returns and the neurons begin to function on a principle similar to the conduction method reported in unmyelinated axons (Smith, Blakemore & McDonald, 1981). This resumption of signal processing is felt to be responsible for the remitting nature of the disease. In addition, signal conduction in damaged neurons may also result from partial remyelination - the synthesis of myelin by undamaged oligodendroglial cells (Morell & Norton, 1972). This process is a limited one in that oligodendroglial cells are not capable of increasing in size and are therefore unable to remyelinate plaques of any significant size.

The process described above regarding demyelination is based on neuropathological models involving the peripheral nervous system. Moreover, the normal formation of myelin discussed earlier and shown in Figure 2 represents only that which is believed to occur in the peripheral nervous system. The involvement of the central nervous system with respect to myelin damage and neural functioning as seen in MS is

It has recently been postulated that the remitting cycle of the disease may be due to an intermittent disruption in the opening of the blood/brain barrier, allowing some myelinolytic factor to enter the brain (Barrett, Drayer and Shin, 1985). Increased permeability of the endothelial cells comprising the barrier has been shown to exist for various infectious diseases such as herpes simplex encephalitis as well as psychophysiologic states such as hypertension (Fishman, 1980). Although the findings regarding permeability changes in the barrier are controversial and have been conducted on lower animals such as rats, the transient transportation of macromolecules across the endothelial cells have been observed in MS patients (Fishman, 1980).
still not completely understood.

According to Hashimoto and Paty (1986) the pathological changes found in MS, both in the peripheral and central nervous systems, follow a relatively consistent pattern: inflammation, oedema and swelling, demyelination, and gliosis. However, the site and degree of neural involvement as well as symptomatic expression may vary considerably from patient to patient.

The authors state that the earliest symptomatic lesion found "in MS is probably inflammatory." (Hashimoto & Paty, p.539). Whether or not viral in aetiology, the inflammation leads to oedema and swelling at the neural site involved. At this point, if the symptoms of oedema and swelling continue, demyelination may occur. As noted by Hashimoto and Paty, it is still unclear whether demyelination results from the loss of either myelin or oligodendrocytes.

If the pathological process is halted, partial and/or complete remyelination may occur - as has been demonstrated in the peripheral nervous system. If the process continues, however, the final stage of gliosis is reached. At this stage, inflammation and oedema tend to decrease as plaques form and age (Hashimoto & Paty, 1986). The increase of astrocytes (gliosis) at the sites involved result eventually in the formation of fibral patterns (scars) along the axons. No remyelination is believed to be possible once gliosis occurs and the plaques mature.
It has recently been argued that demyelination does not involve destruction of Schwann cells as was previously assumed (Sumner, 1985). Instead, work with a lipid antigen called galactocerebrosidase, which causes conduction blocks similar to MS, has led to the speculation that demyelination requires an intact Schwann cell. An insult of a Schwann cell due to some pathogen causes the cell to release endogenous proteases within the folds of the myelin sheath. The protease causes lysis of the membrane, leading to conduction block. It is the response of an intact Schwann cell (creation of protease) that causes the demyelination. Destruction of the Schwann cell would preclude any demyelination from occurring.

Despite Charcot's over-encompassing use of the term demyelination there appear to be two distinct types of demyelination: (1) involving damage to all parts of the axon except the distal part of the nerve fibre and (2) the Wallerian type involving all of the fibre (McDonald, 1974). Presumably, some ability to conduct an impulse exists in the first type of degeneration. This in turn raises the question as to whether the conduction block experienced in MS (eg. Donny-Brown & Brenner, 1944: Morgan-Hughes, 1968; Ochoa, Fowler & Gilliatt, 1972; Smith, Blakemore & McDonald, 1981) results not from the inability to excite demyelinated areas, but instead, as a result of an "impedance mismatch" between normal and demyelinated areas (Sears, Bostock & Sherratt, 1978; Waxman, 1978).
B. DISEASE ONSET

Multiple sclerosis is classically characterized by two phases, which are (1) attack and (2) remission. The attack or relapse phase is usually episodic in nature and may be either acute or slowly progressive (chronic) with the latter being characteristic of about 10% of cases (Fog, 1977). Onset tends to be rapid, usually within minutes or hours (McAlpine et al., 1955, 1972) as well as varied according to symptomology. Table 1 provides a summary of the types and frequency of loss generally associated with MS. As is evident from the table, the frequency varies greatly with the most common type being visual and motor disturbances.

During the acute phase, the symptoms expressed by the patient become severe. The patient tends to remain at this level for a period of days or weeks until s/he enters the second stage - that of remission.

In remission, the patient experiences a lessening of the symptoms with a possible return to some previous level of functioning. Although symptoms may fluctuate during this period, the patient's level of functioning remains relatively stable until a relapse occurs. The number of relapses per year may vary greatly (Thygesen, 1953) with no apparent decrease in the relapse rate as the individual ages (Lhermitte, Marteau, Gazengel, Dorda & Deloche, 1973). Furthermore, there does not appear to be a significant correlation between the number of relapses and severity of the attack (Fog & Linnemann, 1970).
### TABLE 1

Major Symptoms Found During the Course of MS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Kuroiwa et al. (1982)(^1)</th>
<th>Kuroiwa et al. (1982)(^2)</th>
<th>Poser et al. (1978)</th>
<th>Field (1977)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=488)</td>
<td>(n=177)</td>
<td>(n=1271)</td>
<td>(n=527)</td>
</tr>
<tr>
<td>Visual</td>
<td>68.7%</td>
<td>63.8%</td>
<td>66.0%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>26.0</td>
<td>44.6</td>
<td>34.0</td>
<td>-</td>
</tr>
<tr>
<td>Optic Atrophy</td>
<td>58.2</td>
<td>57.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>37.5</td>
<td>74.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Balance or Ataxia</td>
<td>40.8</td>
<td>79.7</td>
<td>82.0</td>
<td>76.7(^3)</td>
</tr>
<tr>
<td>Paresis</td>
<td>-</td>
<td>-</td>
<td>88.0</td>
<td>-</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>60.5</td>
<td>77.4</td>
<td>87.0</td>
<td>-</td>
</tr>
<tr>
<td>Bowel or Bladder</td>
<td>59.9</td>
<td>69.5</td>
<td>63.0</td>
<td>19.4</td>
</tr>
</tbody>
</table>

\(^1\) Asian series  
\(^2\) Hungarian series  
\(^3\) Classified under the general heading of cerebellar dysfunction
Regarding the acute phase, Kurtzke (1970) reported that patients who experienced an attack prior to the one upon which the diagnosis was made were less affected by the disease than those patients whose onset bout was the diagnostic bout. The one distinguishing feature of the latter group was the preponderance of motor symptoms. In addition, prognosis appears to be more favourable if the onset bout is also characterized by the presence of optic neuritis (Newell, 1978) - a relationship which will be discussed later.

From the combination of acute and remission phases, there appear to be four general types of disease course (Kraft, Coryell, Freal, Hanan & Chitnis, 1979). The first, the benign course, is found in about 20% of MS patients. It is of an exacerbation (acute) - remission pattern, where recovery is almost complete and subsequent exacerbations are mild and relatively infrequent. Although such patients are not symptom free, they do experience relatively long stable periods, with little or no restrictions placed on their physical and/or mental functioning.

The second type, the exacerbating - remitting course, is characterized by relapses occurring at the rate of one every six months to one every three or four years. Such patients are able to function in an occupation for about twenty years, after which
the majority develop a remitting-progressive course.

The third type, the *remitting-progressive pattern*, is defined by the presence of one or more attacks followed by periods of total or partial remission. Unlike the benign course, the remitting-progressive course is cyclical in nature until the patient reaches a stage where the disease slowly progresses without remission.

The fourth type, the *progressive course*, occurs in a minority of MS patients (about 10%) and is identified by the slow onset of motor weakness. There is no remission of symptoms, resulting in severe disability. Although relapse rate tends to be a distinguishing feature of MS, researchers (e.g., Fog & Linnemann, 1970; Lhermitte, Marteau, Gazengel, Dirda & Deloch, 1973) have not confirmed Thygeson's (1953) reports that there is a significant correlation between number of relapses and severity of the disease.

Despite the apparent ability to define the course of MS, clinicians find it impossible to predict the exact course the disease will take in a patient. In addition, difficulties arise with respect to diagnosing the disease at time of onset as well as its severity. Numerous clinical scales exist for categorizing patients on the basis of mobility (e.g., Thygesen, 1949; McAlpine and Compston, 1952;
Fog, 1964) or neurological signs (disability) (eg. Kurtzke, 1961; Alexander, Berkely & Alexander, 1958; Schumacher, Beebe, Kibler, Kurland, Kurtzke, McDowell, Nagler, Sibley, Tourtellotte & Willman, 1965; McDonald & Halliday, 1977; Bauer, 1980; Poser, Paty, Scheinberg et al., 1983). Although these scales classify patients into categories such as 'clinically definite', 'probable' and 'possible', they differ on which symptoms are indicative of which category - a classification problem which makes it difficult to compare results across studies using different diagnostic scales. Moreover, differences in classification criteria are related to the time at which diagnosis is made. Thus Izquierdo, Hauw, Lyon-Caen, Marteau, Escourolle, Buge, Castaigne and Lhermitte (1985) reported that patients classified with Poser's criteria were diagnosed significantly earlier than with the classification of Bauer. However, there was no difference between classifications for those patients diagnosed as "progressive".

Further complicating attempts to study MS is the presence of silent cases, those patients who are asymptomatic and are only revealed at autopsy. Georgi (1961) reported that of 66 autopsied cases, 12 unexpectedly had MS. Similar results have been reported by Alter (1962), Castaigne, Lhermitte, Escourolld, Hauw, Gray & Lyon-Caen (1981) and Gilbert & Sadler (1981), revealing the presence of widespread demyelination among asymptomatic patients. Although the death rate among MS patients is higher than
that of the general public, epidemiological studies tend to indicate that over fifty percent of MS deaths are due to complications such as pulmonary infection and cardiac disease and therefore may not be detected unless an autopsy is performed (eg. Leibowitz, Kahana, Jacobson & Alter; 1972).

C. MODE OF ONSET

As stated earlier, onset of MS is extremely variable with symptoms developing over a matter of minutes, hours, days, or weeks. McAlpine et al. (1955) reported that of 219 confirmed MS patients, 68.4% had symptoms which developed within one week, 22.8% within one year and 8.8% had their symptoms develop progressively over several years. Table 2 provides the findings of several studies reporting the types of early symptoms found among MS patients. The majority of symptoms involve the sensory system (eg. paraesthesia, optic neuritis) with a smaller percent primarily motor in expression. Although it is tempting to assume that the type of symptom expressed is related to the site and extent of the demyelination, such a correlation has not been conclusively established (Field, 1977; Gilbert & Sadler, 1983).

Attempts made at establishing the presence of prodromal features unique to MS have been unsuccessful, generally
TABLE 2

Early Symptoms Found in MS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Poser et al. (1978) (n=1271)</th>
<th>Kuroiwa et al. (1975) (n=948)</th>
<th>McAlpine et al. (1972) (n=241)</th>
<th>Kurtzke et al. (1968) (n=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>36%</td>
<td>43%</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>13</td>
<td>11</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Balance Problems</td>
<td>23</td>
<td>26</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Paresis</td>
<td>43</td>
<td>22</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>41</td>
<td>26</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Micturation Disturbance</td>
<td>10§</td>
<td>-</td>
<td>5</td>
<td>8§</td>
</tr>
</tbody>
</table>

1 Figures are derived from a literature review
2 Optic neuritis
3 Includes vomiting due to vertigo
4 Classified under a general category called "motor weakness"
5 Includes defecation and sexual disturbances
characterizing the pre-onset period as being pseudo-rheumatic (muscle or joint pains, or neuralgias without fever) or pseudo-neurasthenic (eg. fatigued, irritable) (eg. Abb & Schaltenbrand, 1956). Although recent researchers such as Bervoets & Delaet (1984) have commented upon the neurasthenic feature of MS patients, psychological research has not been able to find an underlying, unitary profile of MS patients. Psychological characteristics of MS patients have ranged from that of euphoria (Sugar & Nadell, 1943; Surridge, 1969), depression and hysteria (Canter, 1951; Shontz, 1955; Whitlock & Siskind, 1980) to that of denial, anxiety and somatic concern (Peyser, Edwards & Poser, 1980).

Pathological findings have revealed the multi-focal nature of the disease. In an autopsy of 70 MS patients, Ikuta and Zimmerman (1976) found plaques in 99% of the optic nerves, 97% in the cerebrum, 87% in the cerebellum, 84% in the midbrain, 98% in the pons, 88% in the medulla and 99% in the spinal cord. Similarly, sclerotic plaques have been reported extensively in the optic nerves, chiasm, and tracts (Walsh & Hoyt, 1969; Lumsden, 1970; Patterson & Heron, 1980). Histological work on the eyes of MS patients have indicated the presence of optic nerve atrophy (Gartner, 1953) and abnormalities in the peripapillary nerve fiber layer (Feinsod & Hoyt, 1975).

Imaging techniques such as computed tomographic (CT) scanning and magnetic resonance imaging (MRI) have indicated
focal decreased brain density, and abnormal enhancement with the main area of involvement being in "the periventricular areas or within the cerebral or cerebellar white matter" (Kirshner, Tsai, Runge & Price, 1985, p.860). Despite the high rates obtained with imaging techniques in detecting the presence of demyelinating plaques (about 85%), the correlation between a positive scan and the duration as well as severity of the disease is nonsignificant — although some researchers have argued that there is a strong correlation with CT contrast abnormality (enhancement) and clinical exacerbation (eg. Barrett, Drayer & Shin, 1985).

Such findings, coupled with others to be discussed, appear to indicate the sensitivity of the visual system to the degenerative effects of multiple sclerosis. Because of the apparent sensitivity of the visual system, the following description of symptomatology will deal briefly with motor signs and then focus primarily on sensory signs.

D. MOTOR/BRAIN STEM INVOLVEMENT

Patients whose plaques appear to center upon the cerebellum or spinal cord frequently refer to themselves as clumsy or their limbs as heavy, stiff, or, when a lower limb is involved, as dragging or flapping (McAlpine et al, 1972). Depending upon the site of involvement, patients may demonstrate diplopia, depression, absence of deep reflexes, focal paresis, muscular wasting, vertigo, ataxia, dysarthria
or, rarely, peripheral facial palsy (Lumsden, 1970; McAlpine et al, 1972). In addition, MS patients with motor/brain stem involvement may exhibit 5th cranial nerve (Trigeminal) loss resulting in facial pain and loss of corneal reflex. Impaired hearing due to paralysis of the tensor tympanic may also occur, but is relatively rare (Chusid & McDonald, 1978).

As the thesis of this study centers entirely upon the visual system, the remainder of this section will focus on motor disturbances affecting the visual system. For a more indepth discussion of motor/brain stem involvement, the reader is referred to McAlpine et al., 1972).

Motor involvement of the visual system centers primarily upon nystagmus and abnormalities in smooth eye movement, both of which have been used as early screening tests for MS (eg. Solingen, Baloh, Myers & Ellison, 1977; Sharpe, Goldberg, Lo & Herishanu, 1980, 1981).

1. **NYSTAGMUS**

Nystagmus, which is found in 70% of cases (Newell, 1978) is either of the jerk or vestibular type. **Jerk nystagmus** involves a quick movement nasalward and a slow, corrective move temporalward (the opposite in the abducting eye). According to Sharpe, Goldberg, Lo & Herishanu (1981), opticokinetic nystagmus, a form of jerk nystagmus where the
slow phase results from fixating on a moving object and the fast phase from mediation by higher cortical centers, can be elicited in MS patients in conditions where it is inhibited in normals (fixed target moves with the head) and is suggestive of lesions in the temporal and occipital lobes (Newell, 1978).

Vestibular nystagmus is a reflexive response to "asymmetric stimulation of the semi-circular canals or their central pathways" (Newell, 1978, p.537). Such patients find it difficult to fixate on some target after movement is stopped, and, if the direction of the nystagmus changes with the direction of the gaze, one may suspect extensive vestibular nuclei involvement (Newell, 1978).

2. SMOOTH EYE MOVEMENT

With respect to saccades and smooth pursuit, MS patients are characterized by increased saccadic reaction time, saccadic inaccuracy, and impaired smooth pursuit, suggesting brain stem and/or cerebellum involvement (McAlpine et al., 1972; Solingen, Baloh, Myers & Ellison, 1977; Field et al., 1980). In addition, paresis of ocular muscles may occur (in at least 25% of cases according to Newell, 1978) as well as diplopia due to palsies of individual muscles or internuclear ophthalmoplegia. Reulen, Sanders and Hogenhuis (1984) reported that, in a sample of 84 MS patients, subclinical eye movement disorders were
found in 80% of the 'definite' cases, 74% of the 'probable', and 60% of the 'possible'. In a sample of 21 optic neuritis patients, only 25% showed any eye movement deficit.

Assessment procedures like the Pulfrich, which is primarily a test of conduction loss in one optic nerve (eg. Frisén, Hoyt & Bird, 1973), require fixation of both eyes; and, are therefore affected by the lack of eye muscle control evident in MS. Indeed, this is undoubtedly true of most visual function assessment procedures requiring fixation - some of which will be discussed later.

E. SENSORY INVOLVEMENT

1. GENERAL

According to McAlpine et. al. (1972), roughly 35% of MS patients exhibit some sensory abnormality. Unfortunately, from a diagnostic standpoint, the sensory signs may be difficult to establish and are less severe than the expressed symptoms would seem to warrant. This incongruity between sensory sign and symptoms may be due to the poor knowledge regarding the aetiology and mechanism involved as well as the subjective nature of patients' descriptions of their sensory symptoms.

Sensory involvement in MS has been recognized as early as 1876 by Layden, and subsequently in 1878 by Erb and 1887 by Oppenheim. The signs, probably associated to some degree
with the site of demyelination, range from paraesthesiae (variously described as a *tingling* or *pins* and *needles* senstation to a *dead* feeling), Lhermitte's sign (an *electric* senstation produced by flexion of neck muscles), bowel and bladder disorders, alteration in taste sensitivities, as well as a decrement in two-point discrimination, vibration sensation, and postural sensation (Kurtzke, 1970; Fogg, 1977; Catalanotto, Dore-Duffy, Donaldson, Testa, Paterson, and Ostrom 1984).

Of particular interest are the symptoms indicating involvement of the visual system. Such patients typically report their vision as *misty, blurred* or *foggy* (Kurtzke, 1970; Moore, 1983). They report transitory fluctuations in acuity, depth perception impairment, the presence of phosphenes, deterioration of light perception and difficulty adjusting to changes in light intensities (Kurtzke, 1970; Newell, 1978; Moore, 1983). The complaint tends to be unilateral, with the symptoms lasting anywhere from less than one day to two weeks or more. Discomfort (pressure) or pain may be present in or behind the affected eye, especially in eye movements involving traction of an inflamed optic nerve (Alpine et al., 1968; Lumsden, 1970; Moore, 1983).

The symptoms, typical of optic neuritis and retrobulbar neuritis, may be presented singly or in combination with other neurologic signs (Kurtzke, 1970) and may be seen in demyelinating diseases (MS, neuromyelitis optica, Schilder's
disease), infections (uveitis, meningitis, tuberculosis) and vascular diseases (arteriosclerosis, giant cell arteritis, pulseless disease) (Newell, 1978).

It should be noted that the distinction between optic neuritis and retrobulbar neuritis appears to vary with authors. Some authors view retrobulbar neuritis as representing demyelination of the optic nerve without visible ophthalmoscopic changes and therefore classify the pathology as optic neuritis (eg. Newell, 1978). Whereas others view optic neuritis and retrobulbar neuritis as clinically separate - optic neuritis referring to changes at the nerve head or optic disc and retrobulbar neuritis to changes in the optic nerve outside the globe (eg. Kurtze, 1970). Differences in the classification of these two clinical conditions among authors makes it difficult to assess the ophthalmological literature on MS.¹

However one defines it, the percentage of MS patients who initially exhibit optic neuritis in the literature ranges from 11.5% (Kurland et al., 1963) to 83% (Haller, Patzld and Eckert, 1980). This high incidence has led authors such as Bradley and Whitty (1968) to speculate that

¹ According to Ebers and Feasby (1983), the relationship between optic neuritis and MS is also confounded by the fact that central serous retinopathy (an accumulation of serous fluid between the retina and retinal pigment epithelium causing a lesion in the retina) and optic neuritis are similar in pattern. As optic neuritis, central serous retinopathy (CSR) tends to occur in young adults "commonly under stress, has a seasonal prediliction, is unilateral, produces visual blurring and a relative central scotoma, improves spontaneously, but may recur" (p.79). Unlike optic neuritis however, CSR appears not to affect colour vision.
51% of patients with optic neuritis are manifesting the first clinical signs of MS. Such clinical generalities may be misleading in that only about 35% of MS patients tend to have visual complaints (Field et al, 1980) and reliance on the diagnosis of optic neuritis alone may increase the chance of false positives. Recent attempts to index optic neuritis with other positive signs for MS by tests such as the erythrocyte unsaturated fatty acid (E-UFA) test have still only indicated that 32% of patients have MS (Cazzullo, Caputo, Bertoni and Zibetti (1980).

2. SPECIFIC

As early as 1870 (Albutt) it has been shown that the optic nerves and chiasm appear to be especially vulnerable to demylinating diseases. Uhtoff (1889), in an ophthalmological examination of 100 cases, reported optic atrophy in 40% of cases and optic neuritis in 5%. Lehoczky (1954) reported optic chiasmal involvement in 11 patients and 9 with optic nerve abnormalities from a total of 20 MS patients. Similarly, Lumsden (1970) reported 100% involvement of the optic nerves, chiasm, or optic tract in 36 MS patients. Computer tomography of optic neuritis (Howard, Osher, & Tomsak, 1980) and MS (Wuthrich, 1980; Lodder, deWeerd, Koetsier and van der Lugt, 1984) as well as the use of nuclear magnetic resonance in MS (DeWitt, Wrag, Kistler, Davis, Brady and Buomanno, 1984) have confirmed the
involvement of the visual system in exceptional acute stages (20-33% of cases).

Examination in vivo of the retinal layer in MS has indicated diffuse and focal damage of retinal axons even among patients who have not reported any visual disturbances (Frisén & Hoyt, 1974). Feinsold and Hoyt (1975) reported two types of fundal abnormality in the nerve fibre layer of 17 MS patients:

- slit-like defects in the arcuate nerve fibres combined with diffuse thinning of the nerve fibre layer,
- diffuse thinning of temporal peripapillary bundles with a lesser degree of thinning in the remaining sectors surrounding the optic disc.

In an extensive ophthalmological examination of 1,728 cases (1,180 were confirmed MS patients), Bervoets and DeLaet (1984) reported the presence of several abnormalities including retinal vein sheathing, optic atrophy, and nystagmus (see Table 3). The presence of venous sheathing (a whitish segmental structure outlining the vein) is controversial with some authors claiming that its appearance is due to non-MS diseases (eg. Field & Foster, 1962). Kurtzke (1970), however, reports that venous sheathing occurs in about 10% of MS patients and that 80% of patients with venous sheathing had MS. Associated with the presence of retinal venous sheathing has been the non-pathognomonic
### TABLE 3

**Neuro-ophthalmological Findings in MS and Non-MS Patients**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Typical MS (n=1180)</th>
<th>Presumed MS (n=270)</th>
<th>Uncertain MS (n=53)</th>
<th>Non-MS Patients (n=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal Vein Sheathing</td>
<td>292</td>
<td>47</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Optic Atrophy</td>
<td>522</td>
<td>91</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>392</td>
<td>73</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>Anterior Internuclear Ophthalmoplegia</td>
<td>87</td>
<td>29</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Convergence Paresis or Palsy</td>
<td>98</td>
<td>19</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>Horner's Syndrome</td>
<td>13</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Extracted from Bervoets and De Laet (1984)
Changes in visual functioning due to periphlebitis retinae (PR) alone appear to be unknown. Rucker (1945) reported the presence of PR in MS, which has since been confirmed through histological examination of MS eyes (eg. Fog, 1965; Toussaint, 1984). Rucker also reported the presence of dot-like opacities, which has since been established as foci of chronic inflammation (Arnold et al., 1984).

More recently Engell, Jensen and Klinken (1985) reported the presence of PR in histological examination of two confirmed MS patients with reduced visual acuity. The authors argued that periphlebitic lesions in the retinae were clinical signs of early plaque formation since disruptions in the blood-brain barrier occurred simultaneously in PR and MS - a stance supported by some (eg. Adams & Dath, 1977) and rejected by others (eg.

1 Periphlebitis retinae (PR), which may also be found in tuberculosis, syphilis, sarcoidosis and more frequently in chorioretinitis (Newell, 1978) is a neovascularization of connective tissue membrane extending into the vitreous (Scheie & Albert, 1977). PR both occurs and resolves itself quickly, presenting segmental, dilated, beaded occluded veins with sheathing or exudation of lymphocytes and plasma cells.

In an extensive histological examination of the eyes of 47 MS patients, Arnold, Pepose, Hepler and Foos (1984) reported the presence of PR in four cases (8.5%). PR was found to be segmental perivenous lymphoplasmacytic infiltration. The authors reported widespread vascular changes in retinal areas among patients who had and did not have PR. Arnold et al. felt that the vascular changes were more widespread (established through vessel permeability with immunoperoxidase) than could be clinically detected.
Oppenheimer, 1976).

Thus the ocular changes found in MS, i.e. PR, may represent a primary phlebitic process which in the central nervous system leads to demyelination.

3. PSYCHOPHYSICAL ASSESSMENT OF MS

The following is a discussion of the major techniques employed in assessing visual function in MS. Although the first procedure to be discussed, evoked potentials, is not a psychophysical procedure per se, it represents the most frequently used method for assisting in the diagnosis of MS and therefore needs to be discussed.

The argument to be developed is that the evoked potential measures only gross functional changes (amplitude and latency). Such a procedure does not, unless modified, permit one to assess the changes occurring in the macular regions - ones which the writer feels provides a more sensitive indication of the presence and severity of MS.

Following the discussion of evoked potentials, the major psychophysical methods of spatial contrast sensitivity, temporal contrast sensitivity, colour vision assessment, and perimetry will be discussed.
F. VISUAL EVOKED POTENTIALS

1. TECHNIQUE.

Since the classical clinical experiment of Halliday, McDonald and Mushin (1972), visual evoked responses (VERs) have become one of the standard diagnostic methods for assessing the presence of MS, i.e. for the detection of some abnormality of the visual system which, with the presence or absence of other clinical signs, may be indicative of MS.

The VER results from changes in the potentials of an electroencephalogram (EEG) due to the presentation of some visual stimulus. As the EEG consists not only of summated electro-cortical activities but also bio-electrical "noise", the evoked response must be obtained by enhancing the signal-to-noise ratio through mathematical filtering techniques such as autoregressive moving averages (ARMA). As such, the validity and reliability of an evoked potential regardless of its stimulus origin (eg. visual, auditory, somatosensory) are highly dependent upon techniques sensitive to temporal shifts and activity outside the time window of interest (Kay & Marple, 1981).

An evoked potential can be characterized as being either transient or steady-state (Regan, 1982). Transient evoked potentials result from responses to abrupt stimuli such as flashes of light whereas steady-state are composed
of harmonics whose frequencies are precisely defined and are recognizable within the brain's background noise. In essence, the onset of a stimulus results in a transitory response that eventually becomes a steady-state potential.

Regardless of whether one is examining a transient or steady-state response, visually evoked responses may be generated through two basic techniques. The first, flash-evoked responses, result from the presentation of multiple flashes (generally 50 to 100 trials) of a diffuse achromatic light to the entire retinae. Luminance levels of the flash appear to depend upon the equipment (e.g., cathode ray tube) used. Flash induced VER tend to consist of complex waveforms with peaks between 50 and 150 msec., and are felt to result primarily from activity in the macula especially in the case of the electroretinogram (Hirose, Wolf & Malin, 1972). Flash transient VERs are believed to be the result of processing either in the retino-geniculo-occipital striate cortex or the brain stem reticular formation prior to its transmission to the occipital cortex (Carlow, 1980).

The flash VER procedure itself is considered to be a relatively insensitive test for assessing normal-abnormal cortical functioning. The generated latency does not seem to be greatly affected by disease onset (unless severe), and suffers from large variability in the latency shift even among neurologically intact normals (Duwaer & Spekreijse, 1978; Neetens, Hendrata & van Rompaey, 1979; Halliday & Mushin, 1980; Bodis-Wollner and Onofrj, 1982). Additionally,
though equally true of all VER methods, flash VERs are
dependent upon factors such as luminance of background and
target, stimulus frequency (time interval), and electrode
placement and wavelength (Regan, 1977; White, White &
Hintze, 1979; Carlow, 1980).

The second technique for generating VERs, pattern
evoked responses, is through the presentation of a reversing
grating (sine or square wave) or checkerboard pattern.
Patterns are presented at the rate of about 1 or 2 per
second with the luminance being dependent upon the equipment
being used, making it difficult to compare results across
studies. The major advantages of pattern over flash VER are
that the former produces consistent waveforms with a
recognizable positive peak and a consistent latency among
normal samples (eg. Halliday, McDonald & Mushin, 1972;
Behrman, Halliday & McDonald, 1972). As with flash, pattern
generated VERs are felt to result from the complex
interaction between the peripheral and central fovea as well
as higher and possibly lower cortical centres.

2. APPLICATION.

With respect to abnormality, the flash and pattern VERs
may be examined for changes in latency, amplitude, wave
form, and distribution of the potentials (McDonald, 1980).
MS is characterized by an increase in latency of the P100
while maintaining a well-preserved wave form unlike glaucoma
or Parkinson's disease (eg. Bodis-Wollner & Onofrj, 1982). Changes in the waveform and reduction in amplitude may also be seen, especially during the acute stages of an attack of optic neuritis (Adachi-Usami, Kellermann & Makabe, 1972; Feinsod, Abramski & Auerbach, 1973; Feinsod & Hoyt, 1975).

Abnormal VERs have been found in anywhere from 38 to 96% of MS cases (Halliday, McDonald & Mushin, 1973; Purves, Low, Galloway & Reeves, 1981; Kupersmith, Nelson, Seiple, Carr & Weiss, 1983). As indicated in Table 4, the delay in VER occurs more often among "probable" and "definite" MS patients as compared with "possible" patients. Although increased latencies in evoked potentials may be seen in other modalities such as somatosensory (Purves et al., 1981; Haldeman, Glick, Bhatia, Bradley & Johnson, 1982; Philips, Potuin, Syndulko, Cohen, Stanley, Tourtellote & Potuin, 1983) and auditory brain stem (Kjaer, 1980; Purves et al., 1981; Green & Walcoff, 1982; Quine, Regan & Murray, 1983; Javidan, McLean & Warren, 1985), the visual system appears to be more sensitive to the effects of multiple sclerosis (McDonald, 1980; Purves et al., 1981).

Abnormalities in the VER have been reported also among clinically definite MS patients who do not exhibit any visual symptoms (McDonald, 1980). Moreover, the effects may or may not appear bilaterally in the affected and unaffected eye (Milner, Regan & Heron, 1974; Ketelaer, 1980).

Recently Nuwer, Visscher, Packwood and Namerow (1985) demonstrated the presence of significantly delayed P100's in
### TABLE 4

Percentage of MS Patients With Abnormal VEP's

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Definite MS</th>
<th>Probable MS</th>
<th>Possible MS</th>
<th>Suspected MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghezzi et al. (1984)</td>
<td>236</td>
<td>84.0%</td>
<td>65.0%</td>
<td>-</td>
<td>31.0%⁴</td>
</tr>
<tr>
<td>Green &amp; Walcoff (1982)</td>
<td>115</td>
<td>82.0</td>
<td>NC¹</td>
<td>NC³</td>
<td>NC</td>
</tr>
<tr>
<td>Purves et al. (1981)</td>
<td>112</td>
<td>91.0</td>
<td>76.0</td>
<td>14.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Kjaer (1980)</td>
<td>99</td>
<td>100.0</td>
<td>70.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lowitzch (1980)</td>
<td>135</td>
<td>83.0</td>
<td>77.0</td>
<td>60.0</td>
<td>-</td>
</tr>
<tr>
<td>Franck &amp; Middleton (1981)</td>
<td>74</td>
<td>86</td>
<td>89</td>
<td>74</td>
<td>-</td>
</tr>
<tr>
<td>Collins et al. (1978)</td>
<td>98</td>
<td>78</td>
<td>50</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Hennerici et al. (1977)</td>
<td>57</td>
<td>94</td>
<td>94</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>Halliday et al. (1973)</td>
<td>51</td>
<td>97</td>
<td>100</td>
<td>91</td>
<td>-</td>
</tr>
</tbody>
</table>

¹Includes abnormalities in latency and amplitude
²No optic neuritis
³NC - unable to be computed from the article
⁴Stimulation with red and black checkerboard
⁵Foveal stimulation only
the VEP's of neurologically normal first degree relatives of confirmed MS patients. The authors argued that although the findings indicate the presence of subclinical demyelination or focal changes in some relatives, the fact that less than 2% of the relatives will develop clinical MS suggests that the changes are not predictive of MS onset.

Despite such relatively high detection rates among MS patients, delay in the first major positive wave (P100) is not diagnostic of the presence of MS. Delays have been reported in glaucoma (Bobak, Bodis-Wollner, Harnois, Maffei, Mylin, Podos & Thornton, 1983; Regan & Neima, 1984), Parkinson's disease (Bodis-Wollner & Onofrj, 1982; Bobak et. al., 1983) and amblyopia (Chiappa, 1980) as well as numerous other pathologies.

Depending upon the procedure and type of MS patient, the one distinguishing feature of MS may be a well preserved wave form as stated earlier.

Kimura (1985) has recently argued that evoked potential procedures are used indiscriminately in clinical settings. According to Kimura, VERs are only useful in classifying known problems such as in the case of definite multiple sclerosis. The major reason for this is that the "temporal correlation between clinical and electrical changes [due to the existence of some pathology] is tenuous at best" as the intertrial reliability of the evoked potentials are "greater than would be expected from the changes due to the disease" (p.78). Similarly McDonald (1980) and Aminoff, Davis and
Panitch (1984), among others, have pointed out that the VER provides evidence of an abnormality as well as its possible general location but can not identify the cause nor its course.

3. MODIFICATIONS.

Attempts to remedy the lack of clinical differentiation in the VER have been numerous and fall within one of three general approaches. The first involves the examination of several modalities. The procedure generally involves the auditory, somatosensory and visual systems in the assumption that their combination will locate the presence of lesions in either the spinal cord, brainstem, visual system, cerebral cortex or some combination thereof. Results have indicated a higher detection rate of abnormality among MS patients than would be the case when only one modality was examined (Green and Walcoff, 1982; Purves et. al., 1983). This appears to be especially true of definite MS where the detection of an abnormality may be about 80 (Ketelaer, 1980) to 97% (Purves et. al., 1983).

Such detection rates in the presence of no other clinical (physical) signs (eg. Hennerici, Wenzel & Freund, 1977; Small, Matthews & Small, 1978) has affirmed the often repeated belief in the presence of subclinical defects, ones to which techniques like the evoked potential appear to be sensitive.
In a study by Feinsod and Hoyt (1975), all 25 of their MS patients (including 10 with no visual signs or symptoms) demonstrated abnormal latencies and waveform in the VER. Seventeen of the 25 patients had an abnormality of the peripapillary nerve fibre layer (slit-like defects in the arcuate nerve fibres, diffuse thinning of the nerve fibre layer, and diffuse thinning of temporal peripapillary nerve fibre bundles), six also had temporal pallor of the disc due to thinning.

Because of the associated VER abnormalities, Feinsod and Hoyt speculated that distortions in the evoked potentials were due to changes in the retinal nerve fibre layer and axons in the optic pathways. The non-uniform effects of MS across patients with respect to the VER may be reflected in the types of subclinical changes in the nerve fibre layers (eg. disturbances of the waveform and latency may depend upon the width of the nerve fibres involved as well as their location).

However, possible abnormal VERs due to changes in the nerve fibre layer are not specific to MS. Glaucoma, which also has been demonstrated to be associated with nerve fibre layer changes retina (Ariksinen, Lakowski & Drance, 1985) has yielded abnormal VERs (Schwartz & Sonty, 1981; Bobak et. al., 1983; Regan & Neima, 1984).

According to Bobak et. al. (1983), in comparing steady-state visual evoked potentials and electroretinograms (ERGs) generated by sinusoidal gratings (2.3 cycles/degree),
both glaucoma and MS patients showed abnormal ERGs under mesopic illumination. The authors claimed that the MS patients showed greater abnormality in the VER latencies (7 of 10 eyes) than with the ERG, (2 of 10 eyes).

However, a re-analysis by this writer of their data, using a t-test for unequal sample sizes, revealed no significant differences between the two groups on VER latency ($t = 0.19$, $df = 11$, $p > 0.05$), nor on VER amplitude ($t = 0.84$, $df = 13$, $p > 0.05$), nor ERG latency ($t = 0.06$, $df = 13$, $p > 0.05$).

These unreported nonsignificant differences between the two pathologies strengthens the belief that, although the underlying processes involved in diseases such as glaucoma and MS are different, their resulting effects on the VER are similar in that one is viewing the summated activity of the visual system - be it at the retina or occipital lobes at some specific time. Indeed, one danger with approaches where multimodalities are examined is that the reported shift in latencies may only be shifts in the orientation of the dipole due to the positioning of the measuring electrodes (Wood, 1982).

The second general approach to improve VER detection of MS is the manipulation of the stimulus presentation. One of the most common involves the comparison between pattern and flash VER (eg. Neetens, Hendrata & van Rompaey, 1980). Pattern VERs are apparently the most sensitive for reasons discussed previously. Similar attempts with pattern and
flash stimuli have been made with ERGs, results of which have been unsatisfactory (eg. Kirkham & Coupland, 1983).

Of particular interest with the pattern procedure has been the use of contrast gratings in generating VERs (eg. Maffei, 1982; Kuppersmith et al., 1983). In using lower spatial frequencies (2 and 6 cycles/degree) Neima and Regan (1984) reported greater VER abnormality among some MS patients for a small stimulus-check size (11 minutes of arc). VER abnormalities were also found among some patients for large stimulus-checks (45 minutes of arc) regardless of spatial frequency. These results parallel Regan's earlier work demonstrating non-selective spatial frequency loss for MS in that patients varied as to which spatial frequency demonstrated the greatest loss.

VER changes due to stimulation of the fovea or periphery are interesting when taken into consideration with the results on nerve fibre layer loss. Hennerici, Wenzel and Freund (1977) reported greater delays in VERs for foveal small-size rectangle stimulation than for normal checkerboard stimulation of the entire retina among MS patients. The authors suggested that foveal stimulation was more sensitive and reliable than the standard clinical practice of stimulating the entire eye, and that the resulting abnormality was due to demyelination of foveal fibres.

From the results by Hennerici et al. it would appear plausible that if the nerve fibre layer is affected earlier
in MS, and if one can image a stimulus to specific damaged areas, then stimulation of these possible pre-symptomatic structural changes may afford one with a technique not only for the documentation of early onset of some disease, but also an index of severity (greater the nerve fibre loss, the greater the VER or ERG abnormality). The limitation of such a method for charting severity may be that there is a limit to changes in an abnormal evoked response once a certain amount of area (nerve fibre layer) has been destroyed.

With respect to foveal versus peripheral stimulation in MS, others have found similar results to Hennerici et. al. but feel that detection (confirmation) of an abnormality is improved when the results from both foveal and peripheral stimulation are combined (eg. Rossini, Pirchio, Sollazzo & Caltagirone, 1979; Diener and Scheibler, 1980). Although luminance is an important factor there are no available studies on how such a variable may affect VERs of MS patients. With respect to colour, only one study by Franck and Middleton (1981) appears to have examined the relationship between colour and VERs. By using black and white squares as well as red ($\lambda 625$ nm) and black squares, the authors reported better detection with the red and black. The results, unfortunately, are difficult to interpret in that the two stimulus patterns were not equated for luminance; therefore one is uncertain as to whether the improved detection was due to the colour (red) or luminance per se.
In a preliminary on-going study by Kozak, King and Drance (1985), retinal stimulation at the foveal region on a single individual produced similar results. As indicated in Figure 3, the red cinemoid filter ($\lambda D$ unknown) produced a well defined waveform that was slightly more latent (average of 81.0 msec) when compared to the VER produced by a white (achromatic) stimulus (79.3 msec). In addition, the red produced a waveform with greater amplitude than the white. Although the two stimuli were of the same size (Goldmann V), the red — despite the claims by the instrument manufacturer — had less luminance than the white and therefore the two were not photometrically equated and thus may have caused the shift in the latency. The similarity in the results of the two studies would suggest that the differences reported by Franck and Middleton may have been due to differences in luminance equivalence rather than differences in wavelength.

The third and final approach in attempting to improve VERs has been the manipulation of the physical state of the patient. Although symptom production in MS patients has been done with methods such as the hot bath (eg. Rolak and Ashizawa, 1984), only fatigue seems to have been done with VER as the dependent variable. Persson and Sachs (1981) fatigued 15 MS patients and 5 normals on a bicycle ergometer prior to their VERs via standard pattern-reversal stimulation. When compared to pre-exercise VERs, exercise produced VERs did not differ with respect to latency. The only noticeable effect was a short lasting reduction in the
Figure 3

VEP from foveal stimulation with a red and achromatic source.
VER amplitude and visual acuity of the MS patients.

If it is possible to generalize from studies varying in patient characteristics and procedures, it appears that visual function is a highly sensitive measure of pathological conditions, and that cones may be involved earlier than the rods. Moreover, it appears that any attempt to focus upon the involvement of the visual system in MS should involve methodology outlined by visual psychophysics in order to assess changes at either the retinal (eg. rods versus cones) or central processing level. Such a paradigm would enforce stricter methodological control (eg. stimulus control), one solely lacking in many studies.

For a more detailed discussion on VERs the reader is referred to Desmedt (1977), Nakayana (1982), and Petsche, Pockberger and Rappelsberger (1984).

G. SPATIAL CONTRAST SENSITIVITY

1. TECHNIQUE

Spatial contrast sensitivity involves assessing the ability of the visual system to resolve sinusoidal or square wave forms varying from 0.5 to 100% contrast. The sensitivity of the visual system to resolve such wave forms is referred to as "contrast sensitivity function" (CSF). The CSF has a well defined form (see Figure 4) with "a maximum value for spatial frequencies of about 0.15 to 0.6 cycles per
Figure 4

Contrast sensitivity for sine wave.
From Lakowski (1982, p.6)
milliradian (c/m rad) or 2.5 to 10 cycles per degree (c/deg) and decreases at both higher and lower frequencies" (Lakowski, 1982, p.6).

Blurring at higher frequencies results from attenuation due to optical abnormalities (eg. refractive errors) and eye movement. As noted by Lakowski (1983), losses at lower spatial frequencies appear to be related to luminance variations in the gratings or retinal size (demonstrated by Regan, Silver and Murray, 1977).

The advantage of examining CSF is based upon the belief that it permits the researcher to identify specific groups of optic nerve fibres - a belief central to channel theorists such as Regan (1982) who hold that the visual system is comprised of parallel processing information channels. Such an approach assumes that one can evaluate specific ganglion cells in the spatial channel by stimulating receptive fields with their respective spatial frequencies, although no electrophysiological evidence exists for this in humans.
2. APPLICATION

Regardless of the theoretical stance taken, CSF has been found to be highly sensitive to the presence of MS (Regan, Silver and Murray, 1972; Bodis-Wollner, Hendley, Mylin & Thornton, 1979; Zimmerern, Campbell & Wilkinson, 1979; Regan, Whitlock, Murray & Beverly, 1980; Regan, Raymond, Ginsberg & Murray, 1981) as well as age-related changes (eg. Lakowski, 1981; Sekuler & Owsley, 1982) and glaucoma (Lakowski, 1981).

Typically, CSF losses in MS occur in both intermediate and low spatial frequencies with some patients showing a loss only in the higher frequencies. These losses tend to correspond to the changes in visual acuity reported by MS patients with a prior history of optic neuritis - the blurring or washing out of their vision. However, visual acuity in itself, as tested in the clinical setting, is not a sensitive measure of visual loss in spatial frequencies (eg. Regan, 1981).

Results from contrast sensitivity testing provide a possible explanation as to why disturbances in vision can occur without being detected through acuity testing. The typical acuity test, such as the Snellen or Landolt Ring Charts are constructed with 100% contrast between the figure and background. As noted by Lakowski (1981), spatial losses are detected more sensitively at lower contrast levels. Indeed, for visual loss to be detected at a high contrast
level of 100% one would probably require extensive cone and rod damage to have already occurred. Early detection of visual loss would therefore necessitate testing at lower contrast levels.

Unfortunately, for diagnostic purposes, losses in the intermediate and low spatial frequencies are not specific to MS as similar losses have been reported in other disease states such as glaucoma (Wolkstein, Atkin & Bodis-Wollner, 1980; Lakowski, 1982).

More recently, Kuppersmith, Seiple, Nelson and Carr (1984) reported losses for three spatial frequencies (1, 4 and 8 cycles/degree) and four orientations (0, 45, 90 and 135 degrees) among 15 MS cases with visual acuities of 20/40 or better. The losses tended to be spotty or multifocal and involved different eyes.

H. TEMPORAL CONTRAST SENSITIVITY

1. TECHNIQUE

Assessment of temporal sensitivity involves the manipulation of the rate in which a stimulus is being presented while constantly maximizing or varying the contrast, creating the critical flicker frequency (CFF). The CFF is that threshold where a flickering light is perceived as becoming constant and can be obtained by one of two general procedures. One, by flickering a light of constant luminance and background
to some part of the visual field, and secondly, in the de Lange method, by mixing a steady light to a set flicker frequency (Lakowski, 1982).

Temporal sensitivity has been shown to be affected not only by diseases such as glaucoma (e.g., Kozousek, 1968) and retrobulbar neuritis (Heron, Regan & Milner, 1974) but also by variables such as luminance, eccentricity, wavelength and age (Lakowski, 1982). The lack of stimulus specification in the literature makes it extremely difficult to compare findings across studies.

2. APPLICATION

With respect to MS, changes in temporal thresholds are seen as resulting from the effects of demyelination on the conduction rate of a neural signal. As noted by Brussell, White, Mustillo & Overbury (1983), changes in temporal thresholds may result from an increase in "conduction velocity and refractory periods, loss of synchrony between stimulation and firing rates, impulse reflection, and cross-talk between fibres" (p.2). Research typically reports reduced CFF among MS patients (Parsons & Miller, 1957; Titcombe & Willison, 1961; Daley, Swank & Ellison, 1979; Regan, 1981).

In a recent article by Mason, Snelgar, Foster, Herron & Jones (1982), CFF losses among 20 MS patients were reported for stimuli varying in luminance and chromaticity. The
authors claimed that temporal losses were greater in the luminance rather than chromatic channel as has been claimed by others (eg. Fallowfield & Krauskopf, 1984). Similar findings have been reported by Alvarez, King-smith & Bhargara (1972). On the basis of their results, Mason et al. concluded that demyelination was non-selective regarding its effects on nerve fibres in the visual system. In conducting the experiment the authors assumed that, on the basis of the literature, "abnormalities in temporal response [was] associated with the short wavelength sensitive mechanism" (p.247), the blue cone system. Then, inexplicably, they used a red (630 nm) and green (560 nm) light-emitting diode subtending 10 minutes of arc on a white background of 290 cd/m². Their findings with long and middle wavelength LEDs can not be used to reject the hypothesis that chromatic channels are selectively affected. In order to reject the hypothesis, the authors should have used a short wavelength LED. The fact that Mason et al. did not use a blue stimulus may be due to the present unavailability of reliable short wavelength LED.

What can be concluded from the Mason et al. study is that at high background luminances there are deficits in CFF for both chromatic and luminance channels. Since losses are evident in the red system, which might indicate severe or quite progressed damage (eg. Pinckers, Pokorny, Smith & Verriest, 1979) the non-significant difference between chromatic and luminance CFF may be reinterpreted as
indicating that the cone system had already been affected to
the extent that any subsequent damage would result in
minimal functional losses.

In examining the effects of myelin loss in retrobulbar
neuritis, Alvarez (1985) reported losses in spectral flicker
detection, chromatic function, and visual acuity. Although
no information was provided on the instrumentation nor types
of loss (hues) Alvarez argued that myelin loss was
characterized by moderate to severe damage to the colour
opponent system as well as conduction block.

Other attempts to measure temporal changes in MS have
centered upon perceptual delay whereby the perceived delay
in the onset of two synchronously presented achromatic
stimuli are assessed under photopic conditions. The task of
the subject is to adjust the onset of one of the two stimuli
until they appear synchronous. MS and retrobulbar neuritis
patients both demonstrate greater delay times (at least 30
msec.) necessary for perceiving the two stimuli as
synchronous than normals (Heron, Regan & Milner, 1974;
Regan, Milner & Heron, 1976).

With the use of a 0.3 degree target, results from the
technique referred to as delay campimetry can be graphed so
as to create temporal delay fields of the retina. The
results typically reveal greater irregularities in the
temporal fields of MS patients than normals (see Figure 5).

As demyelination does not appear to account entirely
for the conduction losses seen in MS patients (eg. McDonald
Figure 5

Delay campimetry fields on a MS patient. The darker the area, the greater the delay. Modified from Mustillo, Brussell & White (1984).
& Sears, 1970; Bodis-Wollner & Onofrj, 1982), Regan (1983) has argued that the results obtained in delay campimetry (temporal) demonstrate not only neural conduction problems but also differential response (temporal) at the retinal ganglion level (Regan, 1983). The implications of Regan's findings for the retina are difficult to interpret as great variability in temporal ranges across the retina exists even among normals. What needs to be examined is possibly not the mean temporal differences but the range of the variances under specific psychophysical conditions (eg. level of luminance).

Modifications of delay campimetry, multi-flash and double-flash campimetry, where the subject responds to detect the presence of flicker in two stimuli presented at the same retinal location, has yielded similar results in demonstrating greater latencies among MS, retrobulbar neuritis, glaucoma and retinitis pigmentosa patients (eg. Galvin, Regan & Herron, 1976; White, Bross, Mustillo & Borenstein, 1982; Regan, 1983; White, Brussel, Overbury & Mustillo, 1983). Both multi-flash and double-flash campimetry yield temporal fields with islands of impaired temporal sensitivity, shown in Figure 6.

Recently, in a comparison of spatial versus temporal techniques, Overbury, Brussell, White, Jackson & Anderson (1983), reported that the temporal channel demonstrated greater losses than spatial for patients having amblyopia, cataract, optic neuritis or macular degeneration. Although
Figure 6

Impaired temporal sensitivity fields in a normal and MS patient. Darker areas indicate greater delay. Modified from Regan (1981, pp. 240-241)
they claimed multi-flash campimetry was more sensitive than Goldmann perimetry in detecting losses, the conclusion is unsupported in that the kinetic perimetry method employed was done at different luminance values than the temporal. Moreover, the two techniques are so different in methodology, subject bias (eg. greater anticipatory effects in kinetic perimetry, for once a stimulus is sensed its direction and presence is always known) and psychophysical function being assessed that it is difficult to understand why the authors felt the two procedures should have provided similar results.

Finally, one other temporal technique used to assess visual delay in MS has been the Pulfrich Phenomenon (eg. Frisén, Hoyt, Bird & Weale, 1973; Ell & Gresty, 1982) wherein there is a greater delay among MS patients than normals for perceiving an elliptical movement of a stimulus presented in a frontal plane. Rather unexpectedly, Ell and Gresty (1982) reported the phenomenon in the eye of a monocular MS patient. As the effect requires binocular vision, the finding of Ell and Gresty may be either an indication of some gross retinal anomaly in their patient unrelated to the MS or a methodological problem.
I. COLOUR VISION

Of the possible sensory qualities of vision that one may assess, colour vision appears to be affected at an earlier stage by pathologies involving the visual system—be that involvement direct as in optic neuritis or indirect as in the treatment of arthritis. Thus, acquired losses in colour vision have been reported in numerous clinical conditions such as glaucoma (Flammer & Drance, 1984; Drance & Lakowski, 1983; Lakowski, 1981; Lakowski & Drance, 1979), diabetes (Roy, McCulloch, Hanna & Mortimer, 1984; Begg & Lakowski, 1980; Lakowski, Aspinall & Kinnear, 1972), rheumatoid arthritis (Lakowski, Haining & Partridge, 1968), retinitis pigmentosa (Wolf, Scheiber & Paschke, 1980; Robertson & Moreland, 1980) and cerebral lesions (Dubois-Poulson, 1982). Due to the extreme sensitivity of the retinal cone system, losses have also been reported in normal aging (Lakowski, 1958, 1962, 1964), changes in pupil diameter (Ourgaud, Vola, Jayle & Daud, 1972; Lakowski & Oliver, 1973), luminance contrast (Verriest, 1963) and drug intake (Alken, 1982; Alken & Schnabel, 1982; Lagerlöf, 1982).

Colour vision may be classified according to origin, mechanism, or performance (Pokorny, Smith, Verriest & Pinckers, 1979). When classified according to origin, colour vision abnormalities are viewed as either congenital or acquired.
1. SYSTEMS OF CLASSIFICATION

a. I. Classification By Origin

a) **Congenital**: Congenital colour vision losses are due to the presence of some defect in the cone system at the time of birth, the assumption being that the cone system never functioned normally throughout that individual's development. Congenital defects include the red-green and yellow-blue variety (discussed in section III on Classification by Performance) as well as the achromatopsias.

Achromatopsia or monochromacy refers to the condition whereby either the cone or rod system is missing entirely. Rod monochromats are characterized by their inability to differentiate stimuli on the basis of hue alone—resulting in the so-called "colour blind" individual. In addition, rod monochromats tend to be photophobic, have poor acuity, and suffer from nystagmus. Although post mortem examination of a rod monochromat has revealed the presence of cones (Glickstein and Heath, 1975), it is generally felt that the photopigments of achromatopsia subjects have spectral absorption characteristics similar to that of rhodopsin (Boynton, 1979). The presence of rhodopsin-like photopigments may result in the scotopization mechanism felt by Verriest (1964) to
characterize all forms of achromatopsia.

Cone monochromacy may be either of the red (R) cone type or the Blue (B) cone type. Although not discussed here, Weale (1953) has presented evidence for a green cone monochromat. R cone monochromats have spectral sensitivity curves similar to the of deuteranopes except below 500 nm where the R monochromats show higher sensitivity (Alpern, 1974).

B cone monochromats are the most frequent type of cone monochromats. According to Boynton (1979) they have relatively poor acuity, photopic spectral sensitivity similar to the blue cones in normals, and a "normal" Stiles-Crawford effect - suggesting the presence of other foveal cones.

Congenital colour losses tend to be expressed in a predictable manner (Lakowski, 1969). The losses are typically bilateral and relatively stable over time. Discrimination losses are specific with well defined axes and tend not to be associated with any other visual complaints. Colour naming is characterized by classical confusions (eg. the protanope confusing red for blue-green). According to Pinckers, Pokorny, Smith and Verriest (1979), congenital colour losses are also less affected than acquired dyschromatopsias by target size and illuminance. Smith and Pokorny (1977) have demonstrated that dichromats (acquired) perform like anomalous trichromats when target size is increased.
b) **Acquired**: Acquired colour vision losses are based upon the assumption that at one time of the individual's development his/her colour vision was normal. The subsequent changes in colour vision are due to either normal (e.g. ageing) or abnormal (e.g. glaucoma) processes. Classification of the type of acquired loss, depending upon whether one assesses colour vision on the basis of colour matching performance or wavelength and/or hue discrimination, typically show red-green and yellow-blue axis loss. Losses may also be non-specific, or in the case of the Farnsworth-Munsell 100 Hue Test anarchic. Acquired losses tend not to affect both eyes equally. Colour vision function is unstable over time in that, depending upon the pathology, it may either worsen or improve. There is no clearly defined axis and colour naming is usually good (Lakowski, 1969). Acquired defects are occasionally accompanied with reduced visual acuity and/or visual field loss (e.g. optic neuritis).

b. II. **Classification By Mechanism**

If classified by mechanism, colour vision defects are seen as resulting from either absorption, alteration, or reduction processes. Based upon the early work of von Kries (1905), the type of mechanism responsible for the loss is assumed from colour matches that predict the loss.
b) **Absorption**: In the first possible mechanism, the absorption system, the retina is functionally normal and the colour defects are due to pre-receptoral changes in the lens and cornea (Verriest, 1964; Lakowski, 1962). Although most colour matches will agree with the normal trichromat, some colour vision losses will be evident in the yellow-blue axis.

b) **Alteration**: The second mechanism, the alteration system, is due to differences in one or more of the visual photopigments as compared to the normal trichromat. Abnormalities are detected through changes in photopigment absorption spectra (eg. Wald, 1966; Vos and Walraven, 1971; Ruddock and Naghshineh, 1974).

c) **Reduction**: The reduction system, the third mechanism, is characterized by colour discrimination much worse than those found in the normal trichromat while at the same time accepting any matches made by normals. The reduction system may occur through the loss of one of the normal receptor mechanisms (the König mechanism) or by a collapse or fusion of two receptor mechanisms (the Liber-Fick or Aitken-Liber-Fick mechanism). For a further discussion of this topic the reader is referred to Pickford (1958), Lakowski, (1969), and Pokorny et al., (1979).

d) **Classification by Verriest**: Verriest (1964) has employed three other mechanisms for defining acquired colour vision loss, which are: (1) mesopization, (2)
scotopization, and (3) eccentricity.

Mesopization, originally discussed by Ourgaud and Etienne (1961), describes those colour vision losses that result from the increase in photopic thresholds, causing a reduction in the level of retinal illuminance. Here, the change in colour discrimination (shift in \( V \lambda \)) is equivalent to that seen in normal observers under mesopic adaptation.

Scotopization occurs from the intrusion of rod activity in colour vision. The photopic luminosity efficiency function does not characterize the retinal sensitivity of the observer. Such observers, in the extreme case, have colour discrimination losses similar to that of normals under fully scotopic adapted conditions. Unfortunately, it is presently unclear as to what role the rods might play in contributing to such colour vision matches both for normals as well as individuals suffering from some form of cone degeneration.

Verriest's third mechanism, eccentricity, refers to colour vision losses resulting from the excitation of the parafoveal retina by photopic stimuli. Such individuals, as in the case of strabismic amblyopia, are unable to fixate due to eye movement problems. Because of the eye movement, the image is focussed onto the parafoveal region, resulting in poorer discrimination. According to Verriest (1964) and Laszczyk and Szubinska
There is no specific colour defect associated with eccentrication.

C. III. Classification By Performance

The final method for classifying colour vision anomalies, and by far the most extensively used, is that through performance. Performance can be categorized according to the axis of loss and severity (mild, moderate, and severe) or on chromatic discrimination tests (Lakowski, 1969). However, the classification most widely used is that based upon colour matching performance with three primaries, from which are derived three general classifications of (a) trichromat, (b) dichromat, and (c) monochromat.

a) Trichromatism: In the case of the trichromat, or normal observer, all three primaries (representing the short, middle, and long wavelengths of the visual spectrum) are required to match any one spectral colour under photopic conditions. In the Wright (1946) system, the three primaries are the three spectral stimuli of 650\(\lambda\) nm (r), 530\(\lambda\) nm (g), and 460\(\lambda\) nm (b). Associated with the trichromatic classification is the largest group of colour vision defects known as anomalous trichromatism.

Anomalous trichromatism refers to the condition where three primaries are needed to match a spectral colour except that the ratio of the mixtures are
different from normals Lakowski, (1969). The defect may be either protanomalous, deuteranomalous, or tritanomalous (to be discussed shortly).

According to Lakowski, the incidence for the protan defect is 1.5% (male and female) and 4.0 - 5.0% for the deutan. The protan defect is characterized by a luminous efficiency involving long wavelengths (Judd & Wyszecki, 1963). Table 5 from Wyszecki and Stiles (1982) provides information on the salient characteristics of the various defects discussed here.

b) Dichromatism: Dichromats require only two primaries to match spectral colours and belong to that group typically referred to as colour deficient (Lakowski, 1969). The defect may be classified into pairs according to the type of colour confusion manifested.

The first pair lies along the red-green axis and is referred to as protanopia and deuteranopia. The terms, literally meaning 'first' and 'second' defect respectively were thus named by von Kries (1924) so as not to infer any physiological mechanisms into the terms. As can be seen in Table 5, protanopia (red defect) is characterized by reduced luminous efficiency at long wavelengths (Wyszecki & Stiles, 1982). Best wavelength discrimination is at about 490 nm (Vos & Walraven, 1971). Of males, about 1.0% are protanopes whereas only 0.02% of females are.
### Table 5

#### Distinguishing features of the major colour defects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Protanomalous</th>
<th>Deuteranomalous</th>
<th>Protanope</th>
<th>Deuteranope</th>
<th>Tritanope</th>
<th>Red Monochromat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color discrimination through the spectrum</td>
<td>Maternally reduced from red to yellowish green but to a varying degree in different cases</td>
<td>Absent from the red to about 520 nm</td>
<td>Absent from the red to about 530 nm</td>
<td>Absent in the greenish blue to blue (445 to 480 nm)</td>
<td>No color discrimination</td>
<td></td>
</tr>
<tr>
<td>Neutral point (i.e., wavelength of monochromatic stimulus that matches a fixed “white” stimulus)</td>
<td>None</td>
<td>None</td>
<td>400–495 nm</td>
<td>495–595 nm</td>
<td>560 and 570 nm</td>
<td>All wavelengths</td>
</tr>
<tr>
<td>Shortening of the red (i.e., reduced luminous efficiency of long wavelengths)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Wavelength of the maximum of luminous efficiency curve</td>
<td>540 nm</td>
<td>560 nm</td>
<td>540 nm</td>
<td>560 nm</td>
<td>555 nm</td>
<td>507 nm</td>
</tr>
<tr>
<td>CIE 1931 chromaticity of the confusion point (dichromats only)</td>
<td>( \lambda_A = 0.747 )</td>
<td>( \lambda_B = 0.253 )</td>
<td>( \lambda_C = 1.080 )</td>
<td>( \lambda_D = -0.000 )</td>
<td>( \lambda_E = 0.174 )</td>
<td>--</td>
</tr>
<tr>
<td>Percentage frequency of occurrence</td>
<td>1.0</td>
<td>4.9</td>
<td>1.0</td>
<td>1.1</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>among males</td>
<td>0.02</td>
<td>0.38</td>
<td>0.02</td>
<td>0.01</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>among females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Wyszecki & Stiles (1982, p.464)
The colour confusion loci and neutral axis for protanopia, and other dichromats to be discussed, can be found in figure 7. The confusion loci defined by the isochromatic lines (straight lines) characterize the defect. Provided there are no luminance differences, two chromaticities falling along a specific isochromatic line will be confused by the colour deficient observer while a normal observer would see them as different as long as there is some minimum difference between the two chromaticities. A line drawn perpendicular to the neutral axis indicate those colours that the dichromat is likely to discriminate.

In the second defect, **deuteranopia**, there is no reduced luminous efficiency of long wavelengths. The neutral point occurs at about λ495 nm and the peak relative luminous efficiency is at 560 nm. Incidence rates are 1.1% for males and 0.01% for females.

The second major pair of colour vision defects is determined from the confusion along the yellow-blue axis, tritanopia and tertartanopia. **Tritanopia** is characterized by an absence of discrimination between 445 to 480 nm (Wyszecki & Stiles, 1982). There is no reduced luminous efficiency at long wavelengths and maximum luminous efficiency is at about 555 nm (Wyszecki & Stiles, 1982). Roughly 0.002% of males and 0.001% of females have this type of defect.
Confusion loci, centre of confusion, and neutral axes for dichromats. From Lakowski (1969, p.187)
Little is known about tertartanopia. Some have argued that such a condition does not exist (Boynton, 1979). However, others such as Muller (1924), Judd (1949) and Lakowski, (1969) have presented theoretical evidence for tertartanopia. Loss in the yellow-blue axis involves two neutral points in the spectrum, one at 465 nm (blue) and 575 nm (yellow). As noted by Lakowski (1969), colours falling along the confusion lines shown in Figure 7 would not be discriminated by such an individual. Theoretically, there should be no reduction in luminous efficiency for long wavelengths. No data is available for the incidence of tertartanopia.

c) Monochromatism: The last major classification by colour matching performance is monochromatism. Monochromats, be they rod or cone, need only one primary (as well as luminance information) to match any spectral colour under photopic conditions. They are unable to discriminate any colour at all and are identified only by either their photopic (cone) or scotopic (rod) relative luminousity functions. The defect is extremely rare. Information on rod monochromats estimates the frequency to be 0.003% among males and 0.002% among females. No data is available on the frequency of cone monochromats.

In all, it needs to be stressed that colour vision defects should not be seen as separate categories (eg. dichromat versus trichromat) but instead as a continuum
ranging from excellent colour discrimination to no discrimination at all. Only by doing so does one get a better understanding of the process known as colour vision.
2. ASSESSMENT OF COLOUR VISION

The assessment of colour vision may be done through colour matching and hue or wavelength discrimination (Δλ). Another approach, that of determining the photopic efficiency of the cone system to spectral energy (Ελ), will be dealt with in the section on perimetry.

a. Colour Matching

Colour matching involves the mixing of spectral colours to produce a specific match to some reference. The procedure, typically done laboriously on a colorimeter such as Wright's Colorimeter, is used to determine what ratios of the three primaries (r, g, b) are required to match a given wavelength. Normal trichromats are able to match all hues with an appropriate mixture of the three primaries. Deviations in the type of primaries and their ratios needed provide an estimation of the type and severity of colour vision loss.

Colour matching performance can be assessed relatively easier on colorimeters called anomaloscopes (eg. the Pickford -Nicolson Anomaloscope). Subjects view a bipartite field and match one half of the field with the other on the basis of brightness and spectral composition. Colour vision may be examined on red-green,
yellow-blue, and green-blue ratios.

Anomaloscopes evaluate an individual on specific matches or equations involving the matching of two spectral colours. There are three such equations used to assess colour vision deficiencies, which are: 1) the Rayleigh Equation, 2) the Pickford-Lakowski Equation, and 3) the Engelking Trendelenburg Equation. The Rayleigh and Pickford-Lakowski Equations are the most frequently used.

The Rayleigh Equation discriminates between congenital red-green colour defects. Depending upon the anomalscope used (e.g. the Nagel), the task involves matching a spectral light of about $\lambda_{589}$ nm to a mixture of spectral lights of $\lambda_{670}$ nm and $\lambda_{545}$ nm. The possible range of ratios between $\lambda_{670}$ nm and $\lambda_{545}$ nm a subject uses to match to $\lambda_{589}$ nm is referred to as the matching range, providing the clinician with an index as to the type and extent of the severity. The median point within a range is known as the midmatching point.

The Pickford-Lakowski Equation involves determining the matching range and midmatching point of $\lambda_{470}$ nm and $\lambda_{585}$ nm filtered lights to a white (tungsten) light. The equation was developed to test for age related changes in the yellow-blue range and has proven particularly useful in detecting early acquired losses in various ophthalmological diseases (Lakowski, 1969, Lakowski, 1972).
The final equation, the Engelking Trendelenburg Equation, was developed to assess blue-green losses. The task for the subject is to match a mixture of λ470 nm and λ517 nm to a light of λ490 nm. Figure 8 from Lakowski (1981) shows the location of the various equations on the C.I.E chromaticity diagram as determined from colorimetric information from the Pickford-Nicolson Anomaloscope.

Thus depending upon the equation used, the anomaloscope can, with a high degree of reliability and validity, assess an individual's colour vision. Indeed, many have referred to the anomaloscope as the "queen" of colour vision tests (eg. Boynton, 1979; Working Group 41, 1981).

With respect to assessment using red-green matches, an individual may be classified as a normal trichromat (normal, red-green weak, colour-weak), as a simple anomalous trichromat who may be protonomalous (uses a higher ratio of red to green than the trichromat) or deuteranomalous (more green to red), as an extreme anomalous trichromat who may be either an extreme protonomalous (accepts a large range of red-green matches and has a reduced sensitivity to the red end of the spectrum) or extreme deuteranomalous (wide range for red-green ratio matches including the green primary), or finally as a dichromat (protanope or deuteranope). For a more extensive discussion on colour vision
Colorimetric information on anomaloscope equations based upon the P-N anomaloscope. Modified from Lakowski (1981, p.22)
classifications according to anomaloscopes as well as technique, the reader is referred to Lakowski (1969).

b. Colour Confusion

Although the term colour confusion can be generalized to colour matching (as on the anomaloscope) or hue or wavelength discrimination, it is dealt with separately here inorder to indicate colour vision assessment as done with pseudoisochromatic plates. Colour confusion occurs when an indiviudal mistakes one primary colour for that of another. It reflects the nature of the mistake made. When one discuses the extent of this mistake (how extreme it is), one refers to how poor the matching ratios of that individual is. The concept underlying colour confusion can best be understood in relation to the C.I.E. chromaticity diagram previously shown in Figure 7. The dichromat will confuse two chromaticities that lie on a specific axis with a minimal distance between them, unlike a normal who may perceive the two as different. However if the luminosities of the two chromaticities are the same, the dichromat may not be able to discriminate the two even if the distance between them are great. The discriminating factor here is whether the chromaticities fall along the isochromatic lines for a given dichromat. The isochromatic lines seen in Figure 7 are the confusion loci for that particular dichromat. It is
important to note that although the confusion loci and
directions of the lines may vary slightly from one
individual to another, the confusions for the various
defects are systematic and directional (Lakowski, 1982).

Pseudoisochromatic plates such as the Dvorine,
Ishihara, and Ichikawa's Standard Pseudoisochromatic
Plates are constructed on the principle of colour
confusion. The plates contain figure and ground images
made up of hues that fall along a particular confusion
axis, ones which are confused by an individual with a
specific defect. Thus the pseudoisochromatic plates can
grossly categorize individuals on the basis of their
confusions. Indeed, the validity of these tests can be
assessed by how close the hues on the plates align
themselves to the confusion axis. Colours falling
outside the axis would not be confused and thereby
invalidating the diagnostic discriminability of the
test, as has been shown for example with the Ichikawa
(Lakowski, Young and Kozak, 1981).

c. Hue or Wavelength Discrimination

The term "colour" discrimination refers to the
ability of the observer to discriminate either small,
perceptible differences in surface colours (eg.
Farnsworth-Munsell 100 Hue Test) or spectral or filtered
lights (eg. Koning-Helmholtz monochromator). Unlike the
categorical approach in colour confusion tests
(excluding the anomaloscope), the interval-like approach in colour discrimination procedures recognizes the existence of ranges of discrimination abilities. Utilizing the range (magnitude of error) and the axis of confusion, individuals can be quantitatively and qualitatively assessed on their ability to discriminate colours.

Colour discrimination may be assessed through wavelength discrimination ($\Delta\lambda$), matching ranges based on metameric matches on the anomaloscope, and hue discrimination involving surface colours.

The most extensively used test for assessing hue discrimination is the Farnsworth-Munsell 100 Hue test, and, as mentioned above, it requires the observer to discriminate differences between surface colours.

The FM-100 Hue consists of four boxes containing 85 moveable caps. Each cap consists of Munsell colours that are of equal saturation and brightness, with the only difference being in hue. The boxes cover hues ranging from purple to violet. The caps in each box are presented in a predetermined "randomized" order and the task of the observer is to rearrange them according to their hues.

Error scores are calculated from the misplacements, which are then plotted in either a circular or frequency-by-cap graph form. The degree of lack of discrimination (shown by the size of the error score)
and the location of the errors helps distinguish the type of discrimination problems and its severity. Figure 9 shows the idealized discrimination losses characteristic of the major colour vision defects.

As the discussion of colour vision testing far exceeds the rather brief outline provided here, the reader is referred to the extensive reviews by Lakowski (1966, 1968, 1969, 1982), Boynton (1979), Pokorny, Smith, Verriest and Pinckers (1979), Mollon (1982), and Mollon and Sharpe (1982).

3. APPLICATION

With respect to MS, colour vision losses are prominent among patients with a history of optic neuritis and tend to be of the red-green variety (Cox, 1961; Grutzner, 1972; Vola, Riss, Jayle, Gosset & Tassy, 1972; Scheibner & Thronberend, 1974; Serra, 1982; Kupersmith et. al., 1983). Although the defect is of the protan variety as predicted by Kollner's Law (diseases of the optic nerve result in an acquired red-green defect), it is not classical in that the defect tends to have a deutan component to it (Birch-Cox, 1976).

By far, the majority of research in colour vision has focused upon the use of confusion plates such as the Ishihara. This has probably led to an underestimation of the role colour discrimination may play in assessing both the
Figure 9

Discrimination losses on the FM 100-Hue of the major colour vision defects. From Lakowski (1969, p.274)
presence and severity of optic involvement in MS in that pseudo-isochromatic plates are not particularly useful in measuring acquired colour vision losses (Lakowski, 1981). This is especially true when one recognizes that the standard colour tests done on MS patients involved colour confusion and not colour discrimination.

It has only been within the last decade that attention has focussed upon colour discrimination - mainly surface colours in the Farnsworth-Munsell 100 Hue (FM 100 Hue). Thus Serra and Mascia (1980) reported that virtually all of their MS patients (with or without optic neuritis) showed either yellow-blue, red-green or anarchic type of losses on the FM 100 Hue. The total error score increased significantly if the patient was presently in a state of acute optic neuritis. It is unclear whether patients with a history of optic neuritis differed significantly from those who had no optic neuritis in that the tables provided by Serra and Mascia are not in agreement with their reported sample sizes for the two groups.

Wildberger and van Lith (1976) reported that in the acute phase of optic neuritis (as assessed on the FM 100 Hue and Farnsworth Panel D-15), 6 of 12 eyes had a red-green defect, 2 of 12 eyes blue-yellow, and 4 of 12 eyes were unclassifiable. Four to twenty-four months after the attack, 14 of 20 eyes on the FM 100-Hue and 17 of 20 on the Panel D-15 were normal. In the case of retrobulbar neuritis (RBN), Griffin and Wray (1978) found that all thirty affected and
ten nonaffected (no RBN) eyes, had abnormal scores on the FM-100 Hue even though the patients had a recovery in their visual acuity. No information was made available by the authors as to the nature of the defects. According to Rigolet, Mallecourt, LeBlanc and Chain (1979) and Pokorny et. al. (1979), the major defect in RBN is of a red-green variety and that this defect is highly correlated with other clinical signs such as abnormal VEP's. Similar findings have been reported by Scheibner and Thranbevend (1974).

The interesting feature of MS is that, although it is associated with optic neuritis, MS patients tend not to show a recovery in colour vision. The persistence of the defect over time is equal to that found with RBN.

Serra (1982) reported that in a fatigue design (repeated testing of the FM 100-Hue under an illumination of one Lux) MS patients had worse error scores prior to testing than did the normals. Moreover, the colour defect was more frequently of a tritan type. Fatigue tended to increase the error scores in MS and non-MS patients with optic neuritis, but not normals. This was also true of affected versus unaffected (contralateral) eyes of MS patients (see Figure 10). One intriguing finding was the presence of colour defects in contralateral eyes - a finding that had been reported with RBN (eg. Scheibner & Thranbevend, 1974).

In one of the only investigations on colour discrimination of spectral colours (other studies using incremental threshold procedures will be discussed in the
Figure 10

Effect of fatigue on FM 100-Hue error scores for an MS patient (affected versus unaffected eye). Modified from Serra (1982, p.447)
subsequent section), Lakowski, Harrison and Stell (1985) reported that 70% of MS patients (7 of 10 patients) had colour vision defects as assessed on the Pickford-Nicolson anomaloscope. All were characterized as yellow-blue with half having an additional green-blue loss. Red-green losses were present and showed the greatest difference between MS patients with optic neuritis versus MS patients with no optic neuritis. When compared to ocular hypertensives, the MS patients with optic neuritis had significantly greater red-green losses. MS patients with optic neuritis were found to be similar in their anomaloscope equations to glaucomatous patients, possibly suggesting some similar structural-functional pathology in the two clinical entities. With respect to the FM 100-Hue, losses among the MS patients were found to be anarchic with no defined axis.

Abnormalities in colour vision through the use of spectral colours has also been assessed with the Gunkel Chromograph (Matthews, Kollaritis, Kollaritis, Robinson, Mehelas & Calderone (1983), which involves finding the neutral points for green, magenta, turquoise, red, yellow and blue viewed on a VDT screen. In effect, the Gunkel Chromograph may be viewed as an automated yet instrumentally poorer version of an anomaloscope. MS patients with a previous history of optic neuritis were found to have enlarged neutral areas (larger regions of colours were seen as having no colour) than normals even when visual acuity was 20/20. In another study, Chu, Reingold, Cogan, Hunt and
Young (1983) reported the presence of enlarged neutral areas on the Gunkel for MS patients much greater than those for other patients (see Table 6). They also reported sector defects among MS patients for "orange", "cyan", and "turquoise" (no wavelengths specified).

With a rather unique method known as Flight of Colours (FOC), where subjects describe the colour and brightness of a positive afterimage, differences in perceived "colour" was noted between MS and normals. After the initial stimulation with a coloured light source (about 30 Lux), the subject is blindfolded and requested to report on the afterimage every ten seconds for a period of about ten minutes. Rolak (1984) reported that MS patients with optic neuritis had a shorter duration for the presence of the afterimage than normals and that the FOC correctly identified 126 of 134 eyes. No information regarding the actual durations were provided by the author.

Similar results have been reported by Minderhoud, Smits, Kuks, and ter Steege (1984) in MS patients with a history of retrobulbar neuritis. In addition to the shortened life of the afterimages (less than 175 sec. for MS compared to 278.5 sec. for normals), Minderhoud et al. reported that for MS patients the afterimage duration was especially short for the colours red, purple, and blue. Thirty-one percent of the patients had their afterimages restricted to only one colour or reported none at all.

Unfortunately, no information was provided as to wavelengths
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean Neutral Area Increase (relative to normals)</th>
<th>Major Colour Area Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinitis Pigmentosa (n=38)</td>
<td>14.50</td>
<td>Marked yellow, moderate blue</td>
</tr>
<tr>
<td>Macular Degeneration (n=81)</td>
<td>6.54</td>
<td>Marked yellow, moderate blue</td>
</tr>
<tr>
<td>Optic Neuritis or Atrophy (n=20)</td>
<td>6.08</td>
<td>Mild orange, mild cyan</td>
</tr>
<tr>
<td>Multiple Sclerosis (n=28)</td>
<td>5.54</td>
<td>Moderate orange</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (n=19)</td>
<td>3.46</td>
<td>Mild yellow</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosis (n=68)</td>
<td>2.00</td>
<td>Mild yellow</td>
</tr>
</tbody>
</table>

Modified from Chu et al. (1983)
nor their specific durations.

It is apparent, therefore, that colour vision abnormalities are prevalent in MS. Red-green defects are associated in MS patients with a history of optic neuritis and retrobulbar neuritis and are possibly indicative of either a longer duration or severity of the disease. Unfortunately, no study has been published either longitudinally nor cross-sectionally as to how colour vision may change over time in MS - a change which may hopefully be similar to that observed in different stages of glaucoma (eg. Lakowski, 1981).

J. PERIMETRY
Attempts at assessing visual functioning, especially colour vision in the peripheral retina creates numerous problems. The researcher must be aware of factors such as the rapid decrease in acuity with increasing eccentricity (Aulhorn, 1960), refractive error causing blurred target images with reduced intensity (Aulhorn & Harms, 1972), rapid local adaption (Troxler's effect), changes due to aging (eg. Lakowski & Aspinall, 1969; Verriest & Uvijls, 1977a, 1977b), colour vision defects (eg. Verriest & Uvijls, 1977b; Lakowski, Wright & Oliver, 1977), and poor fixation as well as previous experience of the subject (Aulhorn & Harms, 1972) to name just a few.
Of particular importance, and possibly one of the most problematic, is the question of the effect of stimulus area and stimulus luminance on absolute thresholds. This effect, known under the general heading of spatial summation depends upon numerous factors such as stimulus duration and chromaticity, and will be discussed later.

Despite these intravenous variables, the assessment of "light sense" (Wentworth, 1930) through static and kinetic (dynamic) perimetry has become one of the most valuable methods in both experimental and clinical application. Perimetry has advanced over the years from a purely subjective evaluation of a patient's response to the presence or absence of coloured stimuli presented by the examiner to their stricter evaluation of rod, cone, and rod/cone functioning under specified background and target luminances/wavelengths (Lakowski & Dunn, 1981; Dunn & Lakowski, 1981). Indeed some researchers as Enoch (1978) feel that static perimetry allows one to examine the retina layer-by-layer, providing a completely noninvasive method for localizing and differentiating various retinal/visual pathologies.

As mentioned earlier, the two basic perimetric methods are kinetic and static. Kinetic perimetry differs from static in that the former involves assessing where in the visual field the subject senses a stimulus while luminance (among other variables) remains constant. This process of moving a stimulus from unseen to seen is repeated on various
meridians, resulting in horizontal bearings (isopters) of what Traquair (1949) referred to as the "hill" of vision (see Figure 11).

Static perimetry involves choosing some retinal position to which a stimulus is presented in decreasing and increasing levels of luminance until a threshold is determined. These thresholds (Figure 11) represent the vertical soundings or profiles of the three dimensional hill of vision (Anderson, 1982). Isopter perimetry provides information regarding the shape of visual capacity as well as charting the presence of large, deep depressions (scotomas) whereas profile perimetry enables one to determine the altimetry of a hill, regardless of shape as well as small shallow depressions along a specific meridian. Although profile perimetry could be used to map out the visual field as in isopter perimetry, the process would be too time consuming as it would necessitate measuring thresholds for a number of eccentricities along a large number of meridians.

Thus each method, kinetic versus static, provides the researcher with a specific (isopter versus profile) assessment of the visual field - the method of interest being determined by the problem under investigation. For further information regarding the two techniques the reader is referred to Reed and Drance (1971), Aulhorn and Harms (1972), Tate and Lynn (1977) and Anderson (1982).
Figure 11

Isopter and profile perimetry plots in relation to the retina. Modified from Anderson (1982).
Unlike static perimetry, kinetic perimetry is limited in that the speed at which the stimulus is brought into the field complicates threshold interpretation. Both temporal and spatial summation factors interact in a highly complex manner, which, along with the response speed of the subject, make it difficult to assess which variable or combination thereof is affecting the threshold. Moreover, as kinetic perimetry uses stimuli at suprathreshold values, it is not possible to explore points between two isopters, i.e., relative scotoma are difficult to assess (eg. Verriest & Israel, 1956; Sloan, 1961; Aulhorn & Harms, 1972).

Conversely, static perimetry, with its use of invariant stimulus duration, controls confounding effects due to temporal summation. By manipulating stimulus size, spatial summation effects at different eccentricities can be evaluated (eg. Sloan & Brown, 1962; Dunn & Lakowski, 1981). Of greater importance, from a clinical standpoint, static perimetry enables one to examine field losses (thresholds for specific stimuli such as wavelength and size) under controlled conditions (eg. scotopic vs. photopic). As such, static perimetry affords one with an excellent method for assessing retinal change.

As the clinical literature on MS appear to indicate that the functioning of the macula is the earliest and possibly most affected of the visual systems, it is the belief of the writer that the assessment of retinal sensitivity to chromatic stimuli under specific levels of
preadapatation will provide the most sensitive measure of the presence and severity of MS. Therefore the following sections will focus primarily upon chromatic static perimetry.

1. CHROMATIC PERIMETRY

Chromatic perimetry was first introduced by Aubert as early as 1857 wherein he and Forester studied the distribution of space and colour perception in the visual field (Aulhorn & Harms, 1972). Aubert believed that both space and colour perception were related to "light perception", a belief which became the basis for using stimuli of varying sizes and colours.

Hess (1889), Engelking and Eckstein (1920), and Feree and Rand (1924) employed pigmented targets in examining colour sensitivity and colour defectives. Due to the difficulty in equating pigments, Lauber (1932) introduced the use of interference filters in a projection pathway. These techniques, however, focused upon kinetic perimetry and it was not until Sloan (1939) that 'static' procedures were used to assess light perception at specific retinal positions.

The static method enabled Goldmann (1945a, 1945b) to develop and outline the variables important in modern experimental/clinical static perimetry. Despite these gains, Dubois-Poulsen's (1952) criticisms of chromatic perimetry,
that it did not provide any more information than using achromatic stimuli, effectively stopped research for almost a decade. It was the research by Verriest and his associates (eg. Verriest & Israel, 1965; Francois, Verriest & Israel, 1966; Verriest & Uvijls, 1977) which began to seriously re-examine the use of coloured stimuli in studying normal and abnormal visual functioning. Since then, others such as Hansen (1974), Genio and Friedman (1981), Lakowski, Wright and Oliver (1977) and Lakowski, Drance and Carsh (1980) have extensively studied wavelength sensitivity in normal and abnormal eyes with other techniques such as dark adaptation.

2. THRESHOLD ESTIMATION

Threshold determination in static perimetry for chromatic stimuli can be done through one of three ways: 1) luminance, 2) hue, and 3) flicker (luminance providing 1. Of the three, only luminance and hue will be discussed.

First, as in achromatic perimetry, chromatic perimetry thresholds can be based upon the luminance of the stimulus. Here, where the stimulus is of some specific wavelength, the subject responds when he first detects the presence of the stimulus. The detection is based upon luminance alone and not the wavelength.

In the second method, thresholds are determined from the detection of the hue of the stimulus alone. This second approach, the chromatic threshold, is the most difficult due
to intra-subject variability. Large variability exists in thresholds found through the chromatic detection method due to psychological variables such as knowledge of the wavelengths during testing as well as the saturation level of which the colour must be. This alone, the problem of saturation, is a source of great intrasubject variability.

Equally important, the establishment of thresholds based upon hue are complicated by the photochromatic interval which depends upon wavelength, retinal area, target size, exposure time, and adaptation level as a stimulus shifts from achromatic to chromatic (Aulhorn & Harms, 1972). The time duration of the photochromatic interval depends upon the wavelength, with long wavelengths having the shortest interval and being nearly nonexistant in the fovea. As noted by Aulhorn and Harms, even if one were able to establish reliable chromatic thresholds, they could not be equated to "light perception perimetry" (luminance threshold). The reason for this is that hue differences can be seen even when luminance is constant between two hues. At most, in the case where background and target luminance is constant, one is detecting hue-difference sensitivity and not light sensitivity.

Because of these difficulties, research in chromatic perimetry has centered primarily upon the luminance threshold method in steady state conditions (non flicker).

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1The photochromatic interval refers to the range from absolute rod threshold to the detection of a hue.
Although susceptible to numerous factors as briefly outlined in Table 7, luminance thresholds, when done carefully, yield reliable results with inter-subject variability greater than intra-subject variability. It is a much easier task to detect the presence (intensity) of a light than its presence plus hue. The remainder of the discussion will focus upon achromatic perception of differing wavelengths.

Luminance threshold refers to the noticeable contrast between the luminance of a target and its background. This photometric difference between the two luminance levels may be expressed as;

\[ \frac{\Delta L}{L} \]

Where,

\( \Delta L \) = Difference between stimulus and background luminance

\( L \) = Background Luminance

The reciprocal of the \( \Delta L/L \) provides a measure of differential sensitivity. When speaking of thresholds in terms of intensities as perceived by the observer, the equation can be rewritten into a form described by Weber's Law:

\[ \frac{\Delta I}{I} \]

Where,
### TABLE 7

Factors Affecting Perimetry (Kinetic and Static)

<table>
<thead>
<tr>
<th><strong>Methodological</strong></th>
<th><strong>PreReceptoral</strong></th>
<th><strong>Receptoral</strong></th>
<th><strong>Post Receptoral</strong></th>
<th><strong>Psychological</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Fixation Control</td>
<td>1) Pupil Size</td>
<td>1) Retinal Adaptation</td>
<td>1) C.N.S. Status</td>
<td>1) Motivation</td>
</tr>
<tr>
<td>2) Preadaptation Luminance Level &amp; Duration</td>
<td>2) Ocular Media</td>
<td>2) Visual Angle</td>
<td>- Infections - Infections</td>
<td>2) Past Experience</td>
</tr>
<tr>
<td>3) Background &amp; Stimulus Luminance Level</td>
<td>3) Pigmentation (Iris)</td>
<td>3) Pigmentation (Retinal)</td>
<td>- Tumours - Chemicals - Infections (Learning)</td>
<td>3) Attention Level</td>
</tr>
<tr>
<td>4) Background &amp; Stimulus Wavelength</td>
<td>4) Ocular Structure (eg. Emmetropia)</td>
<td>4) Retinal Eccentricity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5) Stimulus Size</td>
<td>5) Corneal Aberrations</td>
<td>5) Spatial Interactions</td>
<td>2) Ischemic Problems</td>
<td>4) Decision Criterion</td>
</tr>
<tr>
<td>6) Stimulus Duration (On &amp; Off Intervals)</td>
<td>6) Eye Movement (Orbital Muscle Involvement)</td>
<td>6) Temporal Interactions</td>
<td>3) Movement Sensitivity</td>
<td>5) Reaction Time</td>
</tr>
<tr>
<td>7) Threshold Estimation Procedure (eg. Ascending versus Descending)</td>
<td>7) Physiological Status (eg. Presence of nerve fibre layer defects)</td>
<td>7) Differences in Information Processing (eg. Spatial versus Temporal)</td>
<td>4) Personality</td>
<td>6) Personality</td>
</tr>
<tr>
<td>8) Cone/Rod Status (eg. Rod Monochromat)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Committee on Vision (1975), p. 10.
\[ \Delta I = \text{Difference between stimulus and background intensity} \]
\[ I = \text{Intensity of the background} \]

\[ \Delta I/I \] refers to the just noticeable difference required in establishing the relative threshold for a specific stimulus size, wavelength, and eccentricity. The smaller the obtained value, the more sensitive is that particular retinal eccentricity.

Prior to discussing specific variables relevant to establishing relative thresholds, it is necessary to briefly discuss the problem of equating coloured stimulus intensities.

Coloured stimuli may be matched either radiometrically or photometrically. The radiometric method involves specifying stimuli by their physical energy characteristics whereas photometric entails correcting and matching stimuli on the basis of \( \lambda \) (spectral sensitivity of the fovea). Radiometric matching views visual functioning as being equal to the physical characteristics of the organ (the eye) and light. Proponents of the radiometric approach argue that the photometric method is not appropriate as \( \lambda \) is not representative of the entire retina (Aulhorn & Harms, 1972). The difficulty with the radiometric approach, however, is that it is an instrumental - physical method of specifying stimuli. It removes from the researcher the only human
standard available to him, the invariant foveal threshold. In the photometric method where one matches spectral stimuli on the basis of $\lambda$, a \textit{psychophysical} adjustment, the researcher is able to establish \textit{differences} between observers and not remove them as in the radiometric method.

In perimetry involving radiometric matches, findings typically result in high foveal thresholds for red and blue stimuli as compared to achromatic and green stimuli (Aulhorn and Harms, 1972). These relative differences, as noted by Lakowski and Dunn (1981), result entirely from $\lambda$. By removing the effects of $\lambda$ by photometrically equating the stimuli, a psychophysical method, the foveal thresholds would be standardized for luminance, allowing one to assess chromatic sensitivity in the retina (eg. Lakowski, Wright & Oliver, 1976).

Photometric equivalence also plays an important role in the periphery. If not photometrically equated, thresholds in the periphery for chromatic stimuli may vary in sensitivity as well as relative luminous efficiency—a problem which effected earlier researchers discussed by Aulhorn and Harms.

3. \textbf{ADAPTATION}

The luminance level to which the eye has become adapted greatly effects the increment thresholds for chromatic and achromatic stimuli. The effect is presumably due to the complex interaction between luminance, cones and rods.
Unfortunately, due to early experimenter bias and instrument problems, very few studies have been done with chromatic stimuli and adaptation levels.

One of the first examinations of chromatic increment thresholds and luminance background was Wentworth (1930). Using monochromatic stimuli of λ672.5, λ581.5, λ522 and λ468 nm under scotopic conditions, Wentworth reported differential sensitivities across the retina (0 to 180 degrees meridian) for the various stimuli. As seen in Figure 12, the increment thresholds were higher for red and blue than green or yellow in the periphery. Similar results to Wentworth have been reported by Sloan (1939) and Nolte (1962).

With respect to the fovea, a similar relationship was found except that there was little difference between the green and yellow. The implications behind Wentworth's findings are difficult to state in that the difference in the foveal thresholds may have been due to; (1) her use of radiometric units, and (2) the possibility of poor fixation under scotopic conditions resulting in higher sensitivities in the parafovea (stimuli were 1' 16" of visual angle).

Under photopic conditions using stimuli of equal intensities but not size, Nolte (1974), Verriest and Israel (1965) and Ronchi and Galassi (1976) among others reported the presence of a central scotoma for increment thresholds with a "blue" stimulus. No such scotoma, however, was found by Lakowski and Dunn (1979) when the chromatic and
Figure 12

Achromatic thresholds at 0 asb background for 4 monochromatic lights. Stimulus size = 1' 16'
Modified from Aulhorn & Harms (1972, p.122)
achromatic stimuli were photometrically equated and size was kept constant. This finding was not due just to the method of matching but probably more so to the fact that the "blue" scotoma is found with small targets only. In addition to the method by which stimuli were equated, the finding of a "scotoma" for short wavelengths may have been due to problems with fixation. Under scotopic conditions, such as that used by Nolte, fixation becomes difficult to maintain. Any shift in fixation will result in higher sensitivities at adjacent parafoveal areas, thereby creating a relative scotoma.

Again photometrically equating their stimuli, Lakowski and Dunn (1981) reported that differences in the gradients for a blue (475 nm), green (582 nm), red (630 nm) and an achromatic stimulus in the periphery increased as the adaptation luminance decreased. As can be seen in Figure 13, the separation was greatest at the fully-scotopic (rod) level (0 cd/m²). When increased to the fully-photopic (cone) level of 250 cd/m², the gradients were less separated due to the luminosities being photometric equated. The larger shift for the scotopic level was probably due to the Purkinje shift, a shift in sensitivity towards the blue end of the spectrum under scotopic conditions. This difference in relative luminosity efficiency (sensitivity) for rods (510-512 nm) and cones (550-555 nm), shown in Figure 14, became the first psychophysical evidence for a dual receptor system (Duplicity Theory) in the retina. Photopic (Vλ) and
Figure 13

Static thresholds for fully-photopic, mesopic, and fully-scotopic conditions. Stimulus size = 6.8' visual angle, blue (●), green (○), red (△), and achromatic (▲). From Lakowski & Dunn (1981, p.196)
Figure 14

scotopic \( (V\lambda') \) sensitivity greatly effects increment thresholds for chromatic stimuli as seen in the question of radiometric versus photometric \( (V\lambda) \) equivalences and the possibility of rod activity \( (V\lambda') \) in Wentworth's study.

Although researchers such as Wentworth (1930) Wooten and Fuld & Spillman (1975), and Verdun Lunel and Crone (1974) have reported differential sensitivity across the retina for chromatic stimuli under varying background luminance levels, the results by Lakowski and Dunn (1981) are of extreme importance with respect to the fovea.

In addition to the accepted belief that there is an inverse relationship between increment sensitivity and background adaptation even at the fovea, Lakowski and Dunn reported no differential sensitivity for the fovea within adaptation levels except at the mesopic level (blue and red having lower thresholds than the green and achromatic stimuli) as well as the photopic level. As discussed earlier, this finding was opposite to that of earlier research and can be attributed to the author's use of photometric equivalence. Thus, contrary to Hedin and Verriest (1980), increment thresholds under photopic adaptation do not vary greatly with eccentricity for different wavelengths whereas they do in the periphery for red under fully-scotopic conditions. Despite differences in the foveal area, Nolte's (1962) results in the parafovea under mesopic and scotopic adaptation agreed with Lakowski and Dunn (see Figure 13).
4. **SPATIAL SUMMATION**

In addition to adaptation luminance, the size of the stimulus effects increment thresholds. Increment thresholds, depending upon stimulus size, chromaticity and duration, tend to decrease with increasing stimulus size. Various attempts have been made to quantify the relationship as an index of spatial summation would provide one with information on receptive field size.

Aulhorn and Harms (1972) state that luminance and stimulus area are inversely related for thresholds based upon small targets. In the fovea, summation for small targets less than 10' appears to follow Ricco's Law of Complete Spatial Summation (Luminance x Stimulus Area = summation constant). However, in the periphery of the retina, Piper's Law of Partial Summation (Luminance x Stimulus Area\(^{5}\) = summation constant) appears to be true for stimuli up to 1° (Baumgardt, 1972). Although kinetic isopter perimetry has been used to determine summation coefficients (Goldmann, 1945a, 1945b), it should be pointed out that summation ratios should only be established by varying stimulus size at one specific retinal location, removing any temporal effects, i.e. they should be established through static perimetry.

In his research on kinetic perimetry, Goldmann defined the relationship between luminance and area for thresholds as 'k', the exponent of summation. The summation exponent
was defined by Goldmann as:

$$\Phi = \left( \frac{F_0}{F} \right)$$

where \( \Phi \) is the transmittance required from a neutral density filter to maintain a field size with a stimulus of size \( F_0 \), using a stimulus with a size of \( F \). The \( k \) exponent can vary from no summation (\( k=0 \)) to complete summation (\( k=1 \)).

Goldmann reported that, for the kinetic perimeter, a \( k \) value of 0.84 expressed the relationship in his data. Since it is assumed that there is an inverse relationship between luminance and stimulus area, the coefficient of spatial summation can be rewritten as:

$$L \times A$$

To describe a change in \( k \) with a change in stimulus area, the above may be rewritten as:

$$k = \frac{\log L_1 - \log L_2}{\log A_2 - \log a_1}$$

Although the above may be used to provide a measure of spatial summation, it applies only to absolute thresholds rather than increment thresholds for photopic and mesopic levels (Baumgardt, 1972). To estimate the increment thresholds for stimuli of different area, it is necessary to
substitute $\Delta L$ for $L$. In the situation where increment thresholds are obtained at different adaptation luminances, $\Delta L/L$ could replace $L$ as $\Delta L$ is proportional to adaptation luminance. Therefore, using either $\Delta L$ or $\Delta L/L$, $k$ values obtained for absolute thresholds may be estimated for increment thresholds by:

$$k = \frac{\log \Delta L_1 - \log \Delta L_2}{\log A_2 - \log A_1}$$

a. Relevant Literature

Calculating the summation coefficient ($K$) on the basis of the slope and separation between sensitivity gradients, Fankhauser and Schmidt (1958, 1960) and Dannheim and Drance (1971) reported increased summation in the periphery of the retina when compared to the fovea, and that summation decreased with increasing stimulus size. Moreover, they reported an increase in summation with increasing background luminances (0.013-12.7 cd/m$^2$).

Similarly, Sloan (1961) and Sloan and Brown (1962) reported an inverse relationship for achromatic stimuli between stimulus size and increment thresholds using Goldmann sizes of I-V (1/4, 1, 4, 16, 64 mm.). Plotting 'k'

----------

' Note: $k$ here expresses the relationship found under conditions of constant adaptation illumination.
from:

\[ \log L + k \log A \]

Where,

- \( L \) = Luminance threshold
- \( A \) = Stimulus area

Sloan and Brown found that the summation coefficient varied greatly for normals and patients with central serous retinopathy. As with Fankhauser and Schmidt (1958) and Gourgnard (1961), Sloan reported increasing summation in the periphery.

Dunn and Lakowski (1981) investigated spatial summation for chromatic stimuli (red and blue) with Goldmann sizes I, II, III, and IV (1/4, 1, 4, and 16 mm) under fully-photopic, mesopic, and scotopic adaptation. Summation coefficient 'K' was similar for the red (617 nm), blue (474 nm) and achromatic stimuli in the fully-photopic and mesopic conditions. The summation coefficients for red and blue increased with eccentricity and stimulus size. Spatial summation for red and blue, however, varied under scotopic adaptation in that neither changed in a consistent manner for either eccentricity nor stimulus size. Moreover, the red under scotopic adaptation gave larger values for 'K' than did the blue. As noted by the authors, this last finding was probably due to the fact that the two
stimuli were photopically and not scotopically equated. As with previous studies, Dunn and Lakowski reported large variances in the summation coefficients leading them to argue that research should focus upon designs employing equivalent experimental conditions rather than seeking "significance" in its [summation coefficient] absolute value" (Dunn & Lakowski, 1981, p. 205). Thus keeping in mind that intravening variables such as age (general reduction in sensitivity - Lakowski & Aspinall, 1969; Verriest & Uvijls, 1977a), refraction (Aulhorn & Harms, 1972), colour vision abnormalities (Hedin & Verriest, 1980), and knowledge of stimulus position (Engel, 1971) can affect the increment thresholds and therefore the summation coefficient, it is indeed difficult to evaluate the significance of summation as it may only reflect variances in light sensitivity alone.

5. APPLICATION

With respect to MS, virtually all perimetric studies (kinetic and static) report the presence of small relative scotoma both in the periphery and fovea. Serra and Mascia (1982), using an achromatic stimulus in a Goldmann perimeter (size II/2) with an unspecified background found central scotoma in all of their patients with MS. The majority of defects were found among those patients with a previous
history of optic neuritis - a finding found consistently in other research. Profile perimetry results with their patients indicated higher thresholds among recent MS patients in both the affected and unaffected eye. This is equally true of optic neuritis alone (eg. Johnson & Keltner, 1984). Unfortunately, it is difficult to evaluate the results as no information is provided regarding stimulus and background specifications (eg. luminance levels).

Van Dalen, Spekreyse and Greve (1981) assessed the visual fields of 29 MS patients by (1) Friedmann visual field analyzer, (2) kinetic perimetry, and (3) static perimetry. Forty-six eyes of 58 showed abnormal visual fields as well as abnormal VERs. Although no mention was made of stimulus (presumably achromatic) nor background specifications, the authors reported a central defect in six eyes, a central defect and "a defect in the intermediate visual field" (p.80) in 28, and a defect only in the intermediate field in 12. The defects tended to occur only between 10 degrees to 30 degrees eccentricity. Static perimetry (Figure 15) shows a reduced threshold along the 45-225 degree meridian as compared to a normalized curve.

Although Van Dalen et. al. report the presence of patchy, small scotoma 10-20 degrees temporally, the interpretations of this is limited in that no stimulus nor adaptation specifications were provided nor was there any mention of correcting for refractive error. As MS patients with optic neuritis have lowered acuity, one would need to
Static thresholds (45° - 225°) of the right eye (asymptomatic) of an MS patient. Modified from Van Dalen, Spekreyse & Greve (1981, p.81)
know if they were accordingly corrected in the studies mentioned. Moreover, since their figure was of a patient with the right eye, the patchy scotoma in the region of 10 - 20 degrees temporally may have been caused by fixation difficulties shifting the area of the light onto the optic nerve (blind spot).

One consistent finding in this study that has been reported elsewhere (Lowitzsch, 1980) is that Friedman perimetry, involving static thresholds, detected more defects in MS patients than kinetic perimetry. Provided there are no other methodological reasons (luminance levels of background etc.), this difference between static and kinetic perimetry is undoubtedly due to the issues raised earlier.

Meienberg, Flammer and Ludin (1982) examined 14 definite MS patients and 17 normals with the Octopus, an automatic perimeter. Using a target size of 0.43 degrees on a background luminance of 1.27 cd/m$^2$, subjects who were corrected for acuity were examined with programs 33 and 34 (central field with a radius of 30 degrees). Eleven of the thirteen patients had abnormal fields, with the center being spared and losses in sensitivity occurring in the periphery. The defects tended to be patchy relative scotoma between 15 and 30 degrees eccentricity and were shallow in depth. Similar findings with manual perimeters have been reported by Frisén and Hoyt (1974).
Patterson and Heron (1980), using a tangent screen with a background luminance of 2.4 cd/m², reported visual field defects among 46 of 53 MS patients and 12 of 13 optic neuritis patients with no MS. Using an achromatic stimulus (1 mm) moved "centripetally at radial intervals of 30° and at a speed of about 1.5°/sec (p. 205), the authors reported field defects for suprathresholds (target luminance at 172 cd/m²) among 100% of definite MS patients (9/9), 94% of the probable MS (15/16), 81% of the possible MS (13/16), and 75% of the MS patients with no history of visual complaints. Of the defects, 76% were arcuate scotoma, 14% localized depression, 13% generalized depression, and 4% a paracentral scotoma. The high percent of visual field defects among MS patients with no history of visual complaints contradicts the results by Ellenberger and Ziegler (1977) who were unable to find any among 25 similar MS patients. Patterson and Heron argue that the negative findings of Ellenberger and Ziegler was due to their use of the Goldmann perimeter, which they claim can not easily detect narrow relative scotoma. Earlier research using tangent screen have also reported small relative scotoma (central or paracentral) among MS patients (Paton, 1924; Scott, 1957).

Beck, Savino, Schatz, Smith and Sergott (1982) reported homonymous hemianopoea among MS patients, confirming the earlier results of Kurtzke, Beebe, Nagler, Auth, Kurland and Nefzger (1968). Unfortunately, neither study provided information as to the conditions nor specifications under
which the patients were examined on the Goldmann.

Only one study in the literature appears to have focused itself upon increment thresholds for colours. Lakowski (1968) examined the thresholds of an MS patient to two chromatic stimuli, one at 570 nm (cone vision) and the other at 495 nm (rod vision). When dark adapted on a Goldmann/Weekers adaptometer, rod functioning was normal and only during the initial phase of dark adaptation was there any evidence of slight impairment. Examination of the patient on a Goldmann perimeter for static profiles along a horizontal meridian (0 - 180 degrees) under normal levels of adaptation (9.87 cd/m²) revealed extensive retinal threshold losses. As seen in Figure 16, thresholds revealed losses under mesopic and photopic conditions. Foveal sensitivity was reduced by two log units and vision was restricted to 10 degrees eccentricity for photopic adaptation. Thus of the two receptor systems, the cones (photopic) appear to be the most sensitive to the demyelination effects of MS. This is supported by the work of Followfield and Krauskopf (1984) who reported greater threshold losses for MS patients in the chromatic channel (wavelengths not specified) as compared to the achromatic (0.4 log units versus 0.2 for the latter). Subjects were required to respond to changes in chromaticity from white on a background of 300 cd/m². Although no information was provided regarding their respective wavelengths, losses occurred across the four hues (see Figure 17), with the yellow possibly showing more of a loss
Figure 16

Mesopic and photopic thresholds for an MS patient.
From Lakowski (1968, p.97)
Figure 17

Thresholds of colours generated on a television screen for normals and MS patients (affected and unaffected eyes).
Modified from Fallowfield & Krauskopf (1984, p.773)
than the other three.

Although Followfield and Krauskopf employed a different method (television monitor generating their unspecified wavelengths), their reported losses under photopic conditions as well as Lakowski's (1968) for photopic and mesopic clearly indicate the importance of assessing cone functioning in MS.

Similar threshold losses for a red LED stimulus under varying luminance backgrounds having been reported by Patterson, Foster and Heron (1980). Five MS patients were preselected on the basis of having had abnormally variable visual thresholds as previously assessed on an unknown screen (no specifications provided). Wearing neutral density filters, the patients were adapted to a background with either 0, 1.0, 2.0, or 3.0 log cd/m² luminance. Thresholds were established for a red LED (625 nm) subtending 11 degrees and presented in the centre of four small white lights (intensities unknown). Plotted in terms of Frequency of Seeing curves (assumes that the underlying distribution of ΔI is normal), the MS patients demonstrated greater variance in their thresholds across the 1.0, 2.0 and 3.0 log cd/m² adaptation conditions. All of the MS thresholds were significantly higher than those for five normals across all of the adaptation conditions.

Thus it appears that, with respect to perimetry, MS losses appear to be greater under photopic and mesopic conditions. Less variability from normals appear under pure
rod functioning, that is scotopic vision. Though such a statement needs to be carefully guarded due to the lack of precise perimetric specifications in virtually all of the studies reviewed, these results along with the changes seen in colour vision discussed earlier would appear to suggest that static perimetry on cone functioning under mesopic and photopic conditions might provide the means through which both the presence and severity of MS may be evaluated.

6. HYPOTHESIS

A review of the literature has indicated that MS is characterized by both structural and functional changes in the retina. Structurally, MS has shown the presence of optic atrophy, optic neuritis, retinal venous sheathing, and defects in the retinal nerve fibre layer. In addition, imaging techniques (e.g., CT scans) have revealed the extensive presence of plaques in the white matter. More importantly, post mortem examinations have shown a high degree of plaque involvement in the optic nerves.

Functionally, MS patients have shown abnormal evoked potentials with respect to increased latencies and reduced amplitudes -- a finding which appears to be highly consistent for visually evoked potentials. Attempts made at differentiating central versus peripheral visual stimulation with evoked potentials appears to improve detection of MS.
In addition losses have been found for spatial contrast sensitivity in the low and intermediate frequencies, with some MS patients showing high spatial frequency loss. Temporal losses have also been reported, with MS patients exhibiting greater delay than normals. Of luminance and chromatic, there is some evidence to suggest that temporal processing of colour is the most affected of the two.

Probably the most sensitive indicants of the effects of demyelination has been visual assessment through colour vision testing and perimetry. Extensive colour vision losses have been reported among MS patients, with red-green being the most predominant loss as assessed by the anomaloscope. Assessment on the FM-100 Hue has typically shows the loss as anarchic.

Perimetric (kinetic and static) studies with achromatic stimuli have demonstrated the presence of central and peripheral scotoma as well as an overall loss in sensitivity. This appears to be especially true when one examines photopic and mesopic adaptation.

Because of these findings, it is proposed that changes in visual processing due to MS be studied through establishing luminance thresholds for achromatic and chromatic static perimetry on an automated perimeter. It is postulated that MS patients will exhibit greater losses in sensitivity than normals, and that the threshold losses would be dependent upon the adaptational state of the visual system. Earlier threshold loss would be found among MS
patients under photopic or mesopic levels than under photopic.

The types of threshold loss expected are a general reduction in overall sensitivity as well as the presence of scotomas. From the clinical literature, it is expected that the foveal threshold may show the most variability in loss when compared to normals depending upon the state of adaptation. The importance of this assumption, when compared to peripheral thresholds, is that the $\Delta I/I$ between the two functional areas may explain subjective complaints such as glare.

Thus it is proposed that the effects due to demyelination (its presence and severity) in MS be assessed by examining luminance thresholds for chromatic and achromatic stimuli on an automated perimeter. The automatic perimeter is Synemed's Fieldmaster® F225 model, which it is hoped will provide a fast and reliable means for establishing static thresholds. Luminance thresholds will be obtained at both the highest and lowest background bowl luminances possible with the F225. As optic neuritis appears to be closely associated with MS, it is proposed that the MS patients consist of those with and without a history of optic neuritis. MS patients will have been classified into one of three categories by the MS Clinic, Health Sciences Centre Hospital, U.B.C.: 1) clinically definite, 2) probable MS, and 3) possible MS. Attempts will be made to differentiate patients on the basis of clinical stability.
and frequency of episodes (acute phase).

To summarize, it is hypothesized that:

1. Relative thresholds will be significantly different between MS and visually normal subjects and that this difference will be highly dependent upon background preadaptation. Specifically, MS patients will have elevated (higher) thresholds than normals and that the threshold differences between MS and normals will be greater under brighter background adaptation levels.

2. Threshold differences between MS and normals will be greater at and near the fovea than in the periphery.

3. Cone thresholds as determined by red and blue filters will show more selective loss than thresholds determined by the achromatic filter for the MS subjects when compared to normals.
II. INSTRUMENTATION

1. APPARATUS

The Fieldmaster® Model 225 is an automatic perimeter initially designed to provide the clinician with the means to conduct a thorough, standardized assessment of a patient's visual fields. The F225 is equipped with a Digital LSI-11 sixteen-bit computer with 17 factory-installed standard programs and one user-defined program. In addition, there is memory capacity for an additional 81 optional programs that can be factory programmed.

2. PHYSICAL SPECIFICATIONS

The F225 consists of an upright hemispherical bowl, a power supply, and a motorized, height variable table. The bowl is enclosed with the LSI-11 computer and control panel, weighing in total 58.1 kg. The dimensions of the instrument are 88.9 cm in length, 64.8 cm in width, and 119.4 cm in height. The power supply, directly under the table upon which the instrument sits, weighs 28.1 kg and is 91.4 cm by 52.1 cm by 16.5 cm. The table itself weighs 63.6 kg and is 88.9 cm by 71.1 cm by 74.9 cm. More detailed information
regarding the LSI-11 may be found in Appendix A.

The hemispheric bowl has a diameter of 62 cm and includes 149 locations where a stimulus may be presented. Each stimulus location consists of the polished ends of 1 mm diameter fibre optics (visual angle = .19°) that can be selectively illuminated with one achromatic and four chromatic stimuli of varying intensities. Stimulus positions within the bowl are not in a sequential order and therefore when presented to a subject they appear to be 'random'. Control over presentation and bowl background are controlled by the operator through the LSI-11 computer. As is shown in figure 18, the possible positions that can be examined range 70° horizontally and +55° to -65° vertically.

3. CONTROL FUNCTIONS

The operation of the F225 is controlled through a panel on the side of the instrument shell (see Figure 18), which enables the researcher to control both stimulus and background conditions as well as monitor the responses of the subject. The control panel consists of touch sensitive pads and LED display windows for each controllable function.

The stimulus address display window (#1 in Figure 18) presents which stimulus position in the bowl is being presented to the subject. During automatic testing (the running of a standard programme), the LED on the shutter key (#4) will flash. Stimuli may be presented manually by
FIGURE 18

F225 CONTROL PANEL
MODIFIED FROM THE SYNEMED FIELDMASTER F225 MANUAL (P.8)
pressing numbers 1 to 149 on the input keyboard (#14) and then pressing the shutter select key (#4). When the selected position is shown on the stimulus address window (#1), the operator may then press the shutter key to present the stimulus. The shutter will remain open as long as the operator depresses the key, i.e. the stimulus will be presented as long as the key is depressed. It is extremely important that the operator observes that the position he chooses is actually displayed in the address window. Although the shutter light should come on when the shutter is open, at times it will not; and, therefore, the operator should not rely upon the shutter light during automatic testing. If during testing the shutter light is not on and the subject responds, the computer will automatically record the response as positive only if a stimulus has indeed been presented. The type of response recorded (seen or missed) depends upon the choice selected by the operator (#11). The subject’s response is shown as a series of dashes in the display window (#8).

When operating the perimeter manually the operator should take care in that, after a period of more than fifteen minutes of testing, the F225 will not permit the presentation of any more stimuli and will automatically print out results. Although this does not occur all the time, it will cause the operator to lose control of the testing situation and force him to begin again. Discussions with Synemed as to why the computer overrides the operator
during manual mode have not resolved this problem.

The attention monitor (#2) records the general position of the eye. The monitor operates on a corneal reflection method, compensating for both the colour of the patient's iris and background bowl luminance. A photodetector monitors the position of the subject's eye (see Appendix A).

To fixate the eye, the subject is asked to adjust the chin rest until the two red horizontal and vertical lines in the attention monitor are perfectly crossed. This is done by having the subject place his head on the chin rest, with his forehead pressed against the head rest. The subject is then instructed to adjust (or the operator may do this) the adjust slide, tilt, and side clamps. The operator should make certain that the lateral canthus of the tested eye lines up with the edge of the bowl. This is done to ensure that the eye is properly in the field of the bowl. If not, either ask the subject to press his forehead harder against the headrest or adjust the tilt until the lateral canthus is aligned (see Figure 19).

Once the subject is properly aligned, the attention monitor is calibrated by having the subject fixate directly at the crossed red lines and then pressing the Attention Monitor Zero Key (#2) for a few seconds (a green light on the Zero key will come on). Making certain that the stimulus address window shows that position one is in place, the operator then presses the manual shutter button and requests that the subject shifts his gaze to the position illuminated
FIGURE 19
ALIGNMENT OF SUBJECT
MODIFIED FROM THE SYNEMED FIELDMASTER F225 MANUAL (P.19)
in the bowl (5°). Immediately press the Auto Sensitivity Monitor Key. This causes the attention monitor to be readied for subsequent testing, permitting a 5° movement. Anything beyond 5° will cause an alarm to be emitted, which remains on until the subject refixates. For subjects who have lost or are unable to maintain fixation, the operator may reset the attention monitor by just pressing the attention monitor zero key. When the auto sensitivity monitor key is pressed, a value is shown in the attention display monitor. This value, which varies from subject to subject, provides the operator with a baseline from which he may either increase or decrease the sensitivity of the attention monitor to movement in fixation by either pressing the "+" (increase) or "-" (decrease) sensitivity keys respectively.

Although a 5° movement is large for static perimetry, many manufacturers of automated perimeters (eg. Octopus) have adopted the 5° as an acceptable deviation during testing. Despite the psychophysical dubiousness of assuming that such an allowable degree of movement will enable the examiner to validly and reliably assess retinal sensitivity at some specific retinal eccentricity, the 5° was probably agreed upon due to instrumental factors (eg. monitoring fixation through gross techniques as corneal reflection) and subject characteristics (eg. the strenuous demand of good fixation and concentration in standard psychophysical paradigms).
The attention monitor in the F225 has several problems in that it registers any gross head movement or blink as a loss of fixation yet permits a 5° eye movement, one which makes it difficult to establish reliable static thresholds. Moreover, as the attention monitor relies on corneal reflection, it is not possible to do purely scotopic adaptation as the monitor requires a minimal level of light. The monitor functions better with higher background illumination (10 to 35 asb).

The attention monitor presents another problem in that the red fixation lines flash from time to time, which according to Synemed was done purposefully so as to keep the subject's attention trained onto the monitor. Although there is no correlation between stimulus onset and flashing of the lines, subjects do however press the response chord accidentally when the fixation lines flash. To avoid this problem, subjects must be instructed before testing that the monitor flashes and not to respond to it. The attention monitor may be turned off by removing pin 6 (Appendix A) from its socket. To accomplish this task, the interface board with the three connectors must be removed from the backplane in the instrument. This will leave the central fixation target illuminated while power is applied to the instrument. The attention monitor will never blink after pin 6 has been removed. However, the brightness of the fixation target will still remain a function of the background intensity (as in the unmodified condition).
4. STIMULUS CHARACTERISTICS AND PRESENTATION

Stimulus filters are chosen by pressing the appropriate filter key (#3), which causes a filter wheel to rotate over the stimulus light source until the selected filter is in position. The filter wheel consists of five cinemoid filters, which are: 1) a neutral density filter (NDF 1.0), 2) Kodak Wratten #29 red filter (\(\lambda D = 633.73\)), 3) Kodak Wratten #8 yellow filter (\(\lambda D = 581.2\)), 4) Kodak Wratten #61 green filter (\(\lambda D = 535.86\)), and 5) Kodak Wratten #38A blue filter (\(\lambda D = 489.73\)).

The \(\lambda D\) values are presented for illuminant 'A' as the stimulus light source is a 16 watt tungsten bulb. The chief advantages of a tungsten source are stability, continuous spectral output, availability, and high output at about 2854°K for illuminant 'A'. In order to minimize low efficiency due to a problem of heat dissipation from high-wattage sources, the F225 utilizes a low wattage (16 watt) bulb. Thus the actual operating temperature of the tungsten bulb will be well below 3000°K.

The C.I.E. chromaticity coordinates for the various chromatic filters as well as their Tristimulus values and dominant wavelengths may be found in Table 8 for both illuminants 'A' and 'C'. Also presented are the specifications for illuminant D65, a standard laboratory source with more ultraviolet energy than illuminant 'C'.

1 \(\lambda D = \text{Dominant Wavelength}\)
# TABLE 8
COLORIMETRIC SPECIFICATION OF F225 FILTERS

## ACHROMATIC FILTER (NDF)

<table>
<thead>
<tr>
<th>ILLUMINANT</th>
<th>CHROMATICITY CO-ORDINATES</th>
<th>TRISTIMULUS VALUES</th>
<th>DOMINANT WAVELENGTH</th>
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<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>X</td>
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<tr>
<td>A</td>
<td>.455</td>
<td>.414</td>
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</tr>
<tr>
<td>C</td>
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<td>D65</td>
<td>.323</td>
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## RED FILTER (WRATTEN #29)

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<tr>
<td>D65</td>
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<td>.290</td>
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## BLUE FILTER (WRATTEN # 38A)

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## GREEN FILTER (WRATTEN #61)

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<tr>
<td>C</td>
<td>.234</td>
<td>.688</td>
<td>4.17</td>
</tr>
<tr>
<td>D65</td>
<td>.228</td>
<td>.694</td>
<td>4.16</td>
</tr>
</tbody>
</table>
Figure 20 provides the C.I.E. Loci of the various filters for illuminant 'A'. The relative transmittance values for each of the filters may be found in Figure 21. As can be seen from Figure 21, the red filter is a cut off filter restricted to the long wavelength region beyond 600 nm. The remaining chromatic filters, however, are relatively more broad (e.g. the blue containing some of the middle frequencies). The achromatic filter (NDF) transmits and absorbs evenly across the spectrum.

Attempts to photometrically measure the intensity of the presented stimuli have not been successful because of the critical angle at which the measurement has to be made with respect to the head of the fibre optic. This was of prime concern because earlier research with the Fieldmaster 101-PR by Johnson and Keltner (1980) indicated that the luminance meter readings were "lower than actual stimulus luminances by a constant factor of 4.7." (p. 732). Discussions with Synemed® about this revealed that F225 was corrected for this (see Appendix A). Moreover, although the F225 does equate for luminance differences between filters (see Appendix A), this has yet to be confirmed photometrically. Visual, subjective comparison of the filters does indicate the red to be less bright, i.e. transmitt less light than the other filters.

Stimulus intensity in the F225, according the the documentation provided by Synemed, varies from 8.00 asb. to 100,000 asb. in 10.00 asb. steps (or 1 decibel steps). The
G - GREEN  Y - YELLOW  R - RED  B - BLUE
A - ILLUMINANT 'A'

FIGURE 20

C.I.E. CHROMATICITY COORDINATES FOR THE F225 CHROMATIC FILTERS
FIGURE 21

TRANSMITTANCE VALUES OF F225 FILTERS

Legend:
- △ YELLOW wratten #8
- × GREEN wratten #61
- ○ RED wratten #29
- ⊙ BLUE wratten #38a
- ‡ ACHROMATIC ndf
maximum intensity that may actually be obtained is 88,731 asb. for the achromatic filter, 70,985 asb. for the yellow, 17,746 asb. for the red, 8,873 asb. for the blue, and 6,212 asb. for the green.¹

The duration during which a stimulus may be presented ranges from 100 msec. to 9.9 sec. in .1 sec. intervals, and is controlled by entering the desired time through the duration key on the control panel (#10). Interstimulus interval (ISI) is also variable, ranging from 100 msec. to 9.9 sec at .1 sec. intervals. As with the duration, ISI is controlled by entering the desired time with the interval key on the control panel (#10). It should be noted that the ISI chosen by the operator is not the actual one during the running of a threshold or screening programme. The ISI increases as the distance between stimulus positions increases. For example, the examiner may choose to test eight locations in the superior nasal field. Once the desired stimulus intensity, background luminance, filter, attention monitor setting, and stimulus duration and ISI has been selected, the F225 automatically begins to test the preselected locations. The ISI remains constant as long as all eight positions are being examined. When a threshold is determined for a given position, that position is no longer

¹1 apostilb = 0.3183 cd/m². In experimental visual psychophysics one traditionally reports luminance values in terms of candellas (cd/m²). However, as the majority of clinical literature in perimetry refers to luminance in terms of apostilbs, the present study will refer to apostilbs to reduce possible confusion when discussing the literature.
tested and, therefore, the ISI between the preceding and following stimulus locations increases. The reason for this is that stimulus location is processed sequentially. Even if a threshold for some location has been determined, the F225 must sequentially run through that location (without presenting it to the subject) in order to reach the subsequent location. Thus the greater the number of locations whose thresholds already are determined lie between two locations still being tested, the greater will be the ISI between the two. This can be observed by the examiner when viewing the stimulus address window on the control panel.

When a filter is selected by the operator, a neutral density filter situated above the filter wheel automatically compensates for the change in luminance due to filter density (refer to Appendix A). In addition, a correction factor for non-linearity is applied to the stimulus luminance automatically by the LSI-11. It should be noted that high stimulus intensities (above 50,000 asb) are unobtainable with certain filters, such as the red. If this occurs, the stimulus intensity display (#7) will show a series of dashes.¹ problem.

The automatic testing lights (#5) show the operator the status of the perimeter when being run automatically. When the proceed button (#12) is pressed, the testing auto light

¹ It should be noted that any error by the operator or malfunction by the F225 will result in dashes in the display in window question.
comes on and remains on until all the chosen stimulus positions have been run once, at which time the retest light (#5) becomes lit indicating that the positions are to be retested. If the pause key is pressed (#12), the perimeter automatically stops testing and remains inactive (idle light will blink) until the proceed button is pressed again. The reset button automatically resets the perimeter to the beginning stimulus position it began.

5. **BACKGROUND LUMINANCE**

Background intensity in the bowl is controlled by entering the desired luminance level on the input keyboard and then pressing the enter button on the background intensity section of the control panel (#7). The desired level will be registered in the background intensity display (#6). If an error has occurred, dashes will appear in the display and the operator will have to reenter the background value. If the dashes still appear, the background illuminant will have to be replaced.

The illuminant for the background is a General Electric 211-2 bulb. The background bowl luminantion may be set anywhere from 5 asb to 45 asb (1.59 cd/m² to 14.32 cd/m²). Bowl luminantion is constantly monitored and adjusted during testing by a photodiode (Appendix A). As mentioned earlier, bowl luminantion for the attention monitor is best between 10 and 35 apostilbs. An attempt was made to disengage the
background illuminant so that fully scotopic thresholds could be obtained. Unfortunately this was unsuccessful in that the stimulus light source (a tungsten bulb) illuminates the inside back of the bowl, causing all of the 149 stimulus positions to appear bright in contrast with the darkened background bowl.

Photometric measurements of bowl luminance was conducted with a Spectra® Pritchard® Photometer Model 1980A. Measurements were conducted 2 meters from the bowl with a 6 minute measuring field. Three measurements each were done for 20 bowl positions under 8 background luminances. The background luminances were: 1) 2 asb., 2) 5 asb., 3) 10 asb., 4) 15 asb., 5) 30 asb., 6) 45 asb., 7) 50 asb., and 8) 45 asb. Figure 22 shows the photometric results in log apostilbs units for 5 asb., 10 asb., 15 asb., 30 asb., 45 asb., and 50 asb. Results for the 2 and 55 asb. conditions were not included as they did not differ from the 5 and 50 asb. conditions respectively. The actual values for all eight conditions may be found in Appendix B.

The 1 to 20 positions found in Figure 23 represent the points measured in the bowl, as shown in Figure 23. Positions 9 to 20 represent the $15^\circ - 195^\circ$ meridian. As can be seen in Figure 22, this region is relative consistent with respect to background luminance. The nasal position of the bowl (13 - 15) is slightly darker than the temporal region. However, as the difference is less than a log unit, the lower luminance level is not serious. The luminance is
FIGURE 22

BOWL POSITION AND BACKGROUND LUMINANCE
(FOR BOWL POSITION REFER TO FIGURE 23)
FIGURE 23

BOWL POSITIONS MEASURED BY THE PRITCHARD PHOTOMETER
greatly reduced at the point of fixation (position 5), indicating, contrary to the manual, the fixation crosshairs are not correctly adjusted for background luminance. This contrast difference in luminance may effect the determination of thresholds, but since no point is tested with 5°s of this area it may not be of consequence. Unfortunately, there is no way of overcoming this problem given the physical configuration of the bowl.

6. **Threshold Estimation**

Both suprathreshold and threshold profiles may be obtained with the F225. Additional programmes may be stored in the computer (#13 on the display panel). Ten standard programmes are available for determining suprathresholds at various locations in the visual field. The programmes, shown in the programme display window (#9), include an examination of the full visual field (149 positions), a central 30°, a glaucoma screen, a central-cecal, as well as a test of the macula. Appendix C contains the locations for these and other programmes. The actual suprathresholds are printed in terms of isopters similar to that of the Goldmann. Results may be presented as indicating at which intensity the stimuli were seen or not seen.

Suprathresholds are based upon single presentation of a stimulus at some given location (i.e. eccentricity). The DEC computer in the perimeter stores the subject's responses and
later prints out the values upon completion of the examination. As noted by Anderson (1985), this type of suprathreshold testing is primarily adequate for rapidly detecting and establishing types of visual field defects. The procedure, however, neither permits the clinician to establish the density of the defect nor allows him to compensate for changes in retinal sensitivity due to eccentricity (Mills, 1985). Moreover, perimetric assessment may be inadequate for a given subject in that the suprathreshold value (e.g., 50 asb.) chosen may not be optimal for that subject.

Synemed® provides three thresholding procedures to try to overcome the above problems. The first, threshold related testing, allows the examiner to determine the initial intensity by predetermining the subject's actual threshold at some given location. This intensity is then used to determine the suprathreshold profile.

The second procedure available is what Synemed® refers to as contour perimetry. This procedure, more correctly referred to by Mills (1985) and Anderson (1985) as "eccentricity compensated" testing, involves the automatic adjustment of stimulus intensity for eccentricity, i.e., stimuli in the periphery are presented at a higher intensity than stimuli presented centrally.

The F225 has four contour programmes (see Appendix D), each differing as to the "multiplication factor" used to compensate the luminance level. The greater the
"multiplication factor", the more the luminance level is corrected for change in eccentricity. The fourth contour programme (programme #4) is the most desirable as it is the most sensitive to eccentricity, thus reducing examination time quite appreciably.

Each of the four contour programmes may be run in conjunction with any of the F225 suprathreshold or threshold programmes available (except for programme #10 on the macula). Work with the various programmes has led to the conclusion that contour programme #4 should be used whenever possible.

The third suprathresholding procedure used by Synemed® is referred to by Mills (1985) as "defect density" testing. The procedure involves starting at some predetermined suprathreshold level (eg. 50 asb.) and, when not seen by the subject, increasing the intensity until it is seen. Results provide the examiner with a crude record of the possible density of a detected defect. The profile of the defect is crude in that the eccentricity one can test is limited. This problem occurs in both fibreoptic perimeters (eg. the Fieldmaster F225) and LED perimeters (eg. the Dicon 2000 or the Fieldmaster 50).

Apart from suprathreshold examination, the F225 also provides for assessment at the threshold level. Four meridonal profiles are available, and these are: 1) 105 - 285°, 2) 75 - 255°, 3) 165 - 345°, and 4) 15 - 195°. The actual stimulus locations for these four profiles may be
found in Appendix E. It should be noted that neither of the four threshold programmes exceeds 40°. According to Synemed®, the programmes were restricted to 40° in order to shorten testing time as SYNEMED® "found that the information beyond 40° was not needed." (personal communication, July 19, 1982). Whereas limiting the examination to 40° may be appropriate for clinical screening, it is of great importance to go beyond this eccentricity in experimental research since one does not know whether an abnormality may be in the periphery or central regions of the visual field.

In addition to the above four meridional thresholds, a user defined programme (programme #99) provided by Synemed® enables the examiner to determine a threshold for a specific point in the perimetric bowl. Programme #99, however, is limited in the number of stimulus locations that may be assessed during a single testing session.

Thresholds are determined through a bracketing staircase method. The algorithm, shown in Figure 24, involves the initial presentation of a stimulus at some pre-selected level of intensity. The subject's response, based upon pressing or not pressing a button on a response chord, is temporarily stored by the DEC computer along with the presented stimulus level. The F225 then proceeds to the next stimulus position, storing the intensity value along with the subject's response (button pressed or not pressed). When all of the stimulus locations have been tested once, the F225 returns to the stimulus locations it initially
THRESHOLD TESTING ALGORITHM

FIGURE 24
began with and commences to retest all the points.

Depending upon the subject's response, the retest intensity will either be 10.00 asb. higher or lower than the original test intensity. Again, both intensity level and subject response are recorded and the entire process is repeated until thresholds for all locations are computed. A threshold requires the subject to miss a stimulus at a specific intensity twice prior to calculation. The actual threshold value is the average of the intensity level a specific stimulus was seen with the level it was not. Thus, if a subject saw a stimulus 15° nasally at 80 asb. and not at 76 asb., the final threshold for that eccentricity would be 78 asb. Thresholds may be found through either the ascending or descending method depending upon the intensity level at which the examiner commences testing.

Pilot work with the F225 over an initial eight month period has revealed two major faults with such an algorithm for computing thresholds. First, the visual steps of 10.00 asb. for increasing or decreasing stimulus intensity is too large when testing in the fovea.

Secondly, and more seriously, the bracketing staircase method used by the F225 is inappropriate because of a technical fault in the threshold algorithm. When the attention monitor temporarily halts testing because of a blink or movement in fixation, the DEC computer incorrectly assumes that that intensity was "not seen" and therefore increases the intensity during the retest phase. Instead of
retesting that location with the same intensity, the increased intensity falsely raises the subject's threshold. As a threshold is calculated after not seeing a given intensity level twice, this lack of retesting a falsely missed intensity is not serious among those subjects with good or moderate fixation. It does become problematic among subjects with poor fixation or those who blink excessively. Presently, one can only exclude such subjects from testing as they will have artificially raised thresholds. A solution to the problem is to provide one's own algorithm based upon retesting of missed points and smaller increases and decreases in intensity. As the DEC does not permit such flexibility in programming, one will have to interface the F225 with a personal computer capable of controlling the various functions of the perimeter. Appendix F briefly lists how the interface should be done.
7. **INSTRUMENTAL MODIFICATIONS**

As shown in Figure 25 from the Fieldmaster brochure, Synemed® claims that the F225 was capable of providing four meridian threshold profile cuts up to 70° eccentricity both nasally and temporally. Moreover the luminance threshold for the fovea (0° eccentricity) was shown to be about 3 asb. (ΔI/I), providing one an excellent cone profile. When replicated, it was discovered that the thresholds did not exceed 40° eccentricity, that the initial threshold luminance was set at 50 asb., that the ΔI/I value did not approach 3 asb., and that thresholds were unobtainable for any of the chromatic filters other than in suprathreshold testing. Figure 26 provides an example of our results when trying to replicate Synemed's®. Contact with the company revealed that the F225 actually did not provide threshold profiles as they implied in Figure 25 and that the figure was only an idealized version of what they intended their perimeter to do in the future.

As the above problems rendered the perimeter virtually useless for research, the Visual Laboratory entered a long period of interaction between Synemed® of California, U.S.A. and their representatives in Canada, Carl Zeiss Canada Ltd. After eighteen months of repeatedly modifying the instrument, we were able to have the F225 do the following: 1. Present stimuli as low as 8 asb. (we were never able to go lower than this due to a programming problem with
Figure 25

Static threshold profile provided by the Fieldmaster F225 sales brochure (modified from the Synemed Fieldmaster brochure)
FIGURE 26

REPLICATED FIELDMASTER F225 THRESHOLD PROFILE
Synemed®.

2. Conduct threshold testing up to 70° eccentricity both nasally and temporally on a horizontal meridian.

3. Obtain thresholds for the various chromatic stimuli, with assurances that they were photometrically equated.

4. To be able to programme any location in the bowl to be examined for threshold sensitivity.

Despite these modifications to the perimeter, the following problems still exist:

1. Maximum stimulus intensity must be set at a lower level than the perimeter is capable of achieving. Apart from reducing testing time for determining a profile, the major reason for doing so is that after about fifteen minutes of continuous testing the machine stalls and never continues the test. Indeed, upon stalling, the examiner loses all the data that has been stored up to that time. The reason for the stalling is that the algorithm is attempting to increase the stimulus intensity to a level it can never reach, causing the perimeter to interrupt testing. By setting the intensity to some level below its maximum prior to testing, one avoids the problem of stalling and the eventual loss of data.

2. Threshold data is presented in graphic form only. To obtain the actual threshold one must interpolate from the graph with appropriate adjustments (to be discussed later). Although the printout does provide one with an
index of reliability (ratio of correctly seen points over the number presented), individual data regarding intensity level, subject response, and eye movement for each stimulus position throughout the testing session is not provided. To obtain the data, one will be required to interface the LSI-11 to another computer which will retrieve and store the relevant information. Presently, final threshold values are obtainable by connecting a terminal via a RS232-C to the perimeter and accessing the information through ODT (Octal Debugging Technique). ODT provides two sets of octal values (level seen and not seen), which must be transformed into the decibel system prior to computation of the threshold values (see Appendix F).

3. Distraction of subject's by the flashing attention monitor and lack of repeat testing when the attention monitor temporarily stops testing.

During the modifications to the perimeter, three visually normal subjects (mean age of 20.3 years) with 20/20 acuity or better and no known history of retinal pathology were repeatedly tested with programmes #11 and 14 (Appendix E). Testing was done under a variety of background and stimulus conditions. Overall reliability in terms of detection (correct identification of a stimulus) was .93 for the achromatic stimulus, .91 for the red and green, .90 for the blue, and .83 for the yellow. The rates are comparable to those reported for other fibre optic perimeters provided
by Synemed® (eg. Johnson & Keltner, 1980a, 1980b; Gramer, Steinhauser & Kriegstein, 1982).
III. PILOT STUDY

1. PURPOSE

The purpose of the pilot study was to determine whether or not the modifications to the perimeter, discussed in the previous section, would permit one to conduct an assessment of retinal thresholds among MS patients under low (5 asb.) and high (45 asb.) background luminance for the achromatic, red, and blue filters.

2. SUBJECTS

Subjects consisted of one probable (male) and five clinically definite (females) MS patients referred by the MS Clinic in the Acute Care Unit of the Health Sciences Centre Hospital at the University of British Columbia. Seven additional patients were excluded because of either the presence of a large central scotoma \(^1\) or spastic movements making it impossible to position the head and respond. The mean age of the patients was 34.3 years (\( \sigma = 11.4 \)). The average disease duration from the time of diagnosed onset was 12.33 years (\( \sigma = 12.53 \)). Four of the subjects had a history of optic neuritis.

\(^1\) The Fieldmaster ® F225 cannot be used reliably with patients whose scotoma include the fovea and exceed 5°'s temporally or nasally.
3. **METHOD**

Subjects were preadapted for ten minutes under 5 asb. and 45 asb. background luminance conditions prior to testing. The order of the background preadaptation condition was randomized across subjects. Testing, in the case of optic neuritis, was done with the affected eye.

Following a practice session to familiarize them with the task, subjects were tested with programme #98 (dark rectangles found in Figure 27) to determine relative thresholds for a $15^\circ - 195^\circ$ meridian. Eccentricities examined ranged from $40^\circ$ nasally to $70^\circ$ temporally. This meridian was chosen because it provided the most eccentricities near to the traditional $0 - 180^\circ$ meridian profile done in perimetric research. Thresholds were established for the achromatic, red, and blue filters. The order of presentation of the filters was randomized for each background condition for every subject.

Foveal thresholds for each of the three filters, with their presentation randomized, were determined separately after completing the $15^\circ - 195^\circ$ meridian profiles. The thresholds for the fovea were established by having the subject fixate at a point $5^\circ$ nasally in the bowl. Fixation could be monitored by activating the attention monitor similar to normal fixation (fixation set at $5^\circ$ rather than at the fixation target). Thresholds were determined by the repeated presentation of various intensities at that single
FIGURE 27

195 - 15 TEST THRESHOLD PROFILE
(MODIFIED FROM THE SYNEMED FIELDMASTER MANUAL)
5° point. The actual presentation was automatic and achieved by programming the LSI-11 as discussed in the Synemed® manual.

There were two reasons for limiting testing to only the achromatic, red, and blue filters. First, research has indicated that the short (i.e. blue) and long wavelengths (i.e. red) are the most important regions of the visual spectrum to assess functional loss in the cone system. Secondly, the testing time for the three filters under the two background conditions was three hours. Any additional filters would have made the testing more difficult and tiring even for a trained subject.

The stimulus duration for the presentation of each filter was 200 msec. (nearest to the IPS recommendation of 125 msec.). Interstimulus interval was 800 msec. (Synemed® recommended). Thresholds were printed by a thermal graph printer and the actual values were interpolated from an overlaid graph. Each threshold had to be scaled according to the region of the graph on which they were found. Table 9 provide the scalar values required. Subsequent interface of a VDT to the LSI-11 confirmed that the procedure of interpolation and scaling were correct.

4. RESULTS AND DISCUSSION

Results are only presented for the low 5 asb. background condition. The 45 asb. condition will be
<table>
<thead>
<tr>
<th>THRESHOLD POSITION (Y CO-ORDINATE)</th>
<th>SCALAR VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 TO 8</td>
<td>0.33</td>
</tr>
<tr>
<td>8 TO 14</td>
<td>0.67</td>
</tr>
<tr>
<td>14 TO 23</td>
<td>1.00</td>
</tr>
<tr>
<td>23 TO 39</td>
<td>1.78</td>
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<tr>
<td>39 TO 65</td>
<td>2.89</td>
</tr>
<tr>
<td>65 TO 108</td>
<td>4.78</td>
</tr>
<tr>
<td>108 TO 180</td>
<td>8.00</td>
</tr>
<tr>
<td>180 TO 300</td>
<td>13.33</td>
</tr>
<tr>
<td>300 TO 500</td>
<td>22.22</td>
</tr>
<tr>
<td>500 TO 834</td>
<td>37.11</td>
</tr>
<tr>
<td>834 TO 1000</td>
<td>18.44</td>
</tr>
</tbody>
</table>
discussed later. Table 10 provides the means and σ's for the achromatic, blue, and red filters for the various eccentricities. Figure 28 shows the log sensitivity gradients for each of the respective filters. The overall reliability (correct responses) was never below .90.

The results indicated that the lowest stimulus intensity that could be presented was 8 asb. It is apparent, therefore, that the 5 asb. background does not permit one to establish the relative thresholds for the central region of the field (15° nasal to 10° temporal). More importantly, the subjects reached the lower limit of the stimulus intensity (8 asb.) within this central region. Testing with visually normal subjects led to similar findings except that the lower limit extended itself further from the fovea than among the MS patients. Results for a single normal subject may be found in Figure 29.

The limitation of the perimeter to present stimuli lower than 8 asb. greatly effects any examination of foveal functioning. Perimetric research on foveal functioning typically has found the 0° eccentricity, under photopic conditions, to have a threshold less than 1 cd/m² depending upon the stimulus (eg Lakowski & Dunn, 1980). Moreover, incremental steps for assessing foveal sensitivity are generally at .10 log unit steps. With respect to the F225, neither the machine limit of 8 asb. nor the large incremental steps of 10 asb. permit accurate foveal assessment.
<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>ACHROMATIC</th>
<th>RED</th>
<th>BLUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>S.D</td>
<td>MEAN</td>
</tr>
<tr>
<td>NASAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>93.10</td>
<td>76.51</td>
<td>139.14</td>
</tr>
<tr>
<td>30</td>
<td>40.55</td>
<td>9.26</td>
<td>59.23</td>
</tr>
<tr>
<td>20</td>
<td>31.39</td>
<td>18.94</td>
<td>120.10</td>
</tr>
<tr>
<td>15</td>
<td>27.63</td>
<td>20.17</td>
<td>34.75</td>
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<tr>
<td>10</td>
<td>12.02</td>
<td>1.90</td>
<td>18.17</td>
</tr>
<tr>
<td>5</td>
<td>9.07</td>
<td>1.51</td>
<td>14.51</td>
</tr>
<tr>
<td>FOVEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8.00</td>
<td>0.00</td>
<td>8.00</td>
</tr>
<tr>
<td>TEMPORAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
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<td>0.00</td>
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<td>10</td>
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<td>31.06</td>
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<td>7.31</td>
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<td>17.88</td>
<td>5.83</td>
<td>55.34</td>
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<tr>
<td>55</td>
<td>40.16</td>
<td>31.06</td>
<td>71.47</td>
</tr>
<tr>
<td>70</td>
<td>59.10</td>
<td>43.50</td>
<td>140.80</td>
</tr>
</tbody>
</table>
FIGURE 28

SENSITIVITY GRADIENTS FOR MS SUBJECTS
AT 5 APOSTILB BACKGROUND
FIGURE 29
SENSITIVITY GRADIENTS FOR A NORMAL SUBJECT
AT 5 APOSTILB BACKGROUND
5. MODIFICATION TO ADAPTATION

In an attempt to approach the question of adaptation, 6 volunteer MS subjects agreed to participate in a modification of the experimental procedure which allowed the subjects to become readapted at a lower light level (below 45 asb.). Thresholds were determined for the 0° eccentricity both automatically and manually.

In the automated mode, foveal thresholds were determined as outlined in the method section of the Pilot Study. In the manual mode, subjects were instructed to first adapt to the 45 asb. background for ten minutes, after which they were presented with a stimulus below background level (40 asb.). The subjects were then asked to close their examined eye for a period of 2 minutes and not to reopen it until asked. Earlier attempts with shorter time periods had shown that adaptation was not complete.

When instructed to reopen the eye, the subject fixated (him/herself) at the 0° eccentricity again and was retested with either a higher or lower stimulus intensity. Testing always occurred with a 45 asb. background. The procedure was repeated until a foveal threshold was obtained.

After adapting by closing the eye, thresholds were obtained through the descending method of limits. Catch trials of asking the subjects to open his/her eye and not presenting a stimulus were randomly inserted in each test session. Because of time constraints (an additional average
of 20 minutes to the already 3 hour period), only 1 filter could be examined for each subject—except for 1 subject who agreed to 2 testings.

The results for the 2 testing conditions are presented in Table 11. All of the foveal thresholds, except for 1 subject, could be reduced to a lower level from that initially determined in the automatic mode. A dependent $t$-test between the automatic and manual, 2 minute re-adaptation phase revealed that the decrease in threshold was significant ($t=2.37, df=6, p=.05$). Because of the small sample, no comparisons could be made of the 3 filters and the effect changes in adaptation had on them.

When the 2 minute adaptation was tried on normals, there was no difference at all between the automated and manual mode. In both situations, the normals reached the intensity limit of the perimeter (8 asb.), i.e. they reached the limit of the machine.

To examine whether or not the drop in foveal threshold after the 2 minute adaptation period was actually due to a change in adaptation and not rest (fatigue is known to play a major role in psychophysical examinations of MS patients), 3 patients were repeatedly tested at 2 temporal eccentricities ($30^\circ$ and $40^\circ$) with an achromatic stimulus for a period of 30 minutes with no rest. The 2 temporal eccentricities were chosen as there was less chance of finding a scotoma at those positions. A dependent $t$-test between the initial threshold and threshold at the last
### TABLE 11

**FOVEAL THRESHOLD VALUES (APOSTILB) FOR MS PATIENTS DURING ADAPTATION**

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>ACHROMATIC</th>
<th>RED</th>
<th>BLUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORMAL</td>
<td>ADAPTED*</td>
<td>NORMAL</td>
</tr>
<tr>
<td>M.P.</td>
<td>28.34</td>
<td>8.00</td>
<td>-</td>
</tr>
<tr>
<td>P.P.</td>
<td>8.00</td>
<td>8.00</td>
<td>-</td>
</tr>
<tr>
<td>R.C.</td>
<td>14.00</td>
<td>8.00</td>
<td>-</td>
</tr>
<tr>
<td>L.B.</td>
<td>-</td>
<td>-</td>
<td>36.35</td>
</tr>
<tr>
<td>T.M.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S.E.</td>
<td>28.34</td>
<td>8.00</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note: * - 2 MINUTE ADAPTATION CHANGE
testing revealed no significant difference ($t=-3.57$, DF=2, $P>.05$) between the first and last test at 30° as well as at 40° ($t=-0.29$, df=2, $P>.05$). The mean threshold at 40° was 226.83 asb. for the first test and 250.20 for the last. Similarly, the first mean threshold for 30° was 168.00 asb. and 249.76 asb. for the last. If fatigue did play a role then one would have expected the thresholds to have become significantly worse, i.e. become higher over time. According to the means, there was an increase in the thresholds over repeated testing. However, the lack of a significant difference in the repeated testing session would indicate that the improvement seen after having the subjects close their eyes for 2 minutes was primarily due to a change in adaptation level. Further elaboration on this point will be presented in the discussion.

Although adaptation does appear to play a major role in determining thresholds in MS subjects, it was decided to discard the investigation on the effects of lowered adaptation from the present study. The reason for this decision is that the adaptation for the "closed eye" condition would never be known and therefore introduce a methodological constraint on the data. Moreover, by manually trying to investigate the fovea, the F225 continually stalls after a period of 10 minutes. This results in the LSI computer printing an empty thermal graph, after which the operator must restart testing. Periodically the perimeter completely stops functioning, requiring the perimeter to be
turned off and restarted. These problems add unduly to the time required for a subject to remain motivated and prepared for testing.

a. Revised Hypothesis

Based upon the results of the pilot study that demonstrated the inability to examine foveal and peripheral sensitivity due to machine limitation, it was decided to remove the adaptation variable and modify the initial hypothesis as follows:

1. Relative thresholds will be significantly different between MS and visually normal subjects.
2. Threshold differences between MS and normals will be greater at and near the fovea than in the periphery.
3. As a consequence of foveal involvement, cone thresholds for the MS subjects, as determined by the red and blue filters, will show more selective loss than thresholds determined by the achromatic filter.
IV. STUDY

1. SUBJECTS

Subjects consisted of 22 volunteer MS patients referred by the MS Clinic of the Acute Care Unit of the Health Sciences Hospital at the University of British Columbia and 30 age-matched normals with no history of medical problems. The mean age was 32.67 years (σ = 10.86) for the patients, and was 27.50 years (σ = 11.30) for the normals. A t-test for independent groups with unequal sample sizes reveals no significant difference between the ages of the two groups (t = 1.63, df = 49, p > .05).¹

Of the normals, 20 were male and 11 were female whereas 7 of the MS patients were male and 14 were female. A chi-square using Fisher's Exact Test found no significant differences between MS and normals with respect to gender (χ² = 3.33, df = 1, p > .05).²

Ten of the MS patients had a history of optic neuritis and 14 had not. There was no significant difference between the ages of those with or without optic neuritis (t = 0.90, df = 19, p > .05) nor was there a sex difference between the two (χ² = 0.02, df = 1, p > .05).

¹All t-tests referred to are based upon two-tailed tests of probability.
²The Fisher's Exact Tests is Computed for 2 x 2 contingency tables when a cell entry has less than 20 cases.
Fourteen of the MS patients were diagnosed as being clinically definite and eight as probable. Diagnoses were based upon a neurologist's rating of the patient using a modified version of the Rose et. al. (1976) criteria. No age difference was found between the two (t=0.23, df=1, p >.05) nor was there a difference in gender (χ²=.03, df=1, p >.05). There was no difference between the number of patients with or without optic neuritis and their MS diagnostic group (χ²=2.05, df=1, p >.05). Table 12 and 13 provide a summary of the demographic data.

The mean duration of the disease since diagnosis was 10.03 years (σ=8.63) for the entire patient group. The average length since diagnosis for the clinically definite group was 11.85 years (σ=9.82) and 7.43 years (σ=6.35) for the probable. Table 14 provides the means and standard deviations for duration of illness from diagnosis. There was no significant difference between the two clinical groups on duration (t=1.04, df=20, p >.05).

2. PROCEDURE

Subjects were seated at the perimeter and instructed to place their chin on the chin-rest and press their forehead against a restraining bar. Positioning of the head in this way ensured that the lateral canthus of the eye was properly aligned with the edge of the bowl and that the distance from the cornea to the stimulus was held constant at 30 cm.
Table 12

Mean and Standard Deviation for Subjects Categories by Age (Years)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>N</th>
<th>Mean</th>
<th>S.D.</th>
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<tbody>
<tr>
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<tr>
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<td>14</td>
<td>34.15</td>
<td>12.59</td>
</tr>
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TABLE 13
DIAGNOSTIC DEMOGRAPHICS OF SUBJECTS

<table>
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<th>CLINICALLY DEFINITE</th>
<th>CLINICALLY PROBABLE</th>
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<table>
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</tr>
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<td>PROBABLE</td>
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<td>TOTAL</td>
<td>22</td>
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</table>
Once positioned, the subject's fixation on the cross-hairs of the fixation monitor was aligned by adjusting either the height of the perimeter (through a motorized table) or the lateral or vertical position of the head rest.

An opaque white occluder was placed over the non-tested eye. A gauze protective eye pad was inserted between the occluder and eye to reduce the possibility of the subject responding to a stimulus perceived in the periphery of the occluder by the non-tested eye. The F225 is equipped with soft rubber occluders that may be attached to the head-rest and swung into position to cover either the right or left eye. As the occluders do not cover the eye properly and are easily displaced by the subject, the occluders were not used. In the case of the MS patients with optic neuritis, the affected eye was always examined. Only one eye of each subject was tested, resulting in a sample of 22 MS eyes and 30 normal eyes.

Prior to testing, the room was completely darkened and the subject was preadapted to the 45 asb. bowl background for 10 minutes. The subject was instructed to move his gaze around the bowl and not to fixate on the dark central fixation area. In this way, after-images were avoided.

When pre-adaptation was completed, the subject was instructed to fixate upon the center cross-hairs and the attention monitor was set as described earlier in Chapter II on Instrumentation.
Programme 98 was stored in the LSI-11 for the testing of 14 points on the $15^\circ-195^\circ$ meridian, which were: $0^\circ$, $5^\circ$, $10^\circ$, $15^\circ$, $20^\circ$, $20^\circ$, $30^\circ$, and $40^\circ$ nasally; $5^\circ$, $10^\circ$, $20^\circ$, $30^\circ$, $40^\circ$, $55^\circ$, and $70^\circ$ temporally. The size of each stimulus was 1mm., subtending a visual angle of $0.19'$. 

During foveal testing, subjects were instructed to fixate at bowl position #59, which is $10^\circ$ nasal on the $15^\circ-195^\circ$ meridian. The attention monitor was set for this fixation and a two log-unit neutral density filter was placed over the opening of the fibre optic at position #59. The LSI-11 was then programmed to test only at that one point.

The purpose of the two log-unit neutral density filter was to allow for the presentation of a foveal stimulus below the machine limit of 8.0 asb. With the neutral density filter, foveal stimuli could be presented as low as 0.08 asb.

For foveal testing, acuity was corrected by placing trial lenses into a lens holder which is connected to the head-rest. Refractions for the patients were obtained from an ophtalmic technician at the Eye Clinic in the Acute care Unit of the Health Sciences Centre Hospital at the University of British Columbia. Patients with acuities worse than 20/40 were excluded. Similarly, normal subjects were corrected when necessary for foveal testing. Acuity was assessed with the Near Vision Acuity Test for the normals only.
Although pupil diameter is an important variable in perimetry, the diameter was not monitored during testing for two reasons. First, to control pupil diameter, one traditionally uses either an artificial pupil or dilates the pupil prior to testing. Because of the physical configuration of the F225, it would be difficult to use an artificial pupil without greatly affecting the detection of peripheral stimuli.

Secondly, pupil dilation was not chosen as it requires the presence of a medically trained supervisor or approved medical technician, which would have made testing of the normals difficult. Moreover, research has yet to resolve the issue of whether the use of a dilator affects retinal sensitivity.

Prior to testing, subjects received a practice trial to familiarize themselves with the task. Both in the practice trial and actual test trials, subjects were instructed to press the response chord when they saw a light flash, regardless of its colour. Subjects were requested not to respond to the flashing of the cross-hairs on the attention monitor and were shown how blinks and head movements would halt testing.

The order of presentation of the three filters was randomized for each subject in both the 15°-195° and foveal examinations. The foveal examination, with correction for acuity, always followed completion of the 15°-195° exam. Subjects received a five-minute rest after the completion of
each 15°-195° profile and two minutes after the foveal examination. The average length of time for establishing thresholds for the 15°-195° profile was 12 minutes and 1.5 minutes for the fovea. Total test time averaged two hours, depending upon the difficulty encountered in establishing the thresholds.

Thresholds were established through the ascending method of limits with the LSI-11 automatically controlling stimulus duration (200 msec.), interstimulus interval (800 msec.), and luminance intensity in 10 asb. steps. Intensity was also corrected for eccentricity through the use of contour programme #4.

The highest intensity level presented by the F225 was set at 1,000 asb. in order to reduce testing time and the loss of data by having the perimeter stall.

If the threshold level was not obtained at the highest intensity, the subject was given a value of 1,000 asb. for that eccentricity. The lowest intensity obtained in the 15°-195° condition was 8.00 asb. and 0.08 asb. in the foveal condition.

Thresholds were printed, upon completion of testing, in a bar chart format on the thermal printer and the actual threshold values were interpolated as described in the Pilot Study section.
3. RESULTS

The mean reliability of response (correct responses) for normals was 0.93 (σ=0.09) for the achromatic filter, 0.91 (σ=0.11) for the red, and 0.90 (σ=0.11) for the blue. For the MS subjects, the mean reliability was 0.92 (σ=0.10) for the achromatic filter, 0.92 (σ=0.12) for the red, and 0.93 (σ=0.07) for the blue.

Tables 15 to 17 provide the mean thresholds and standard deviations for the 3 groups by filter and eccentricity. Tables 18 to 20 provide similar results for MS subjects with and without optic neuritis.

Figures 30 to 32 show the log apostilb sensitivity gradients for the achromatic, red, and blue filters respectively by subject group. Figures 33 to 35 show the log apostilb sensitivity gradients for the achromatic, red, and blue filters respectively by diagnosis of optic neuritis.

Figures 36 and 37 provide the log apostilb sensitivity gradients for a single MS patient and normal subject respectively. The gradients obtained from the MS patient reveal highly irregular fluctuations across the eccentricities examined unlike that for the normal. These fluctuations are characteristically referred to in the literature as swiss cheese fields. An interesting finding shown in Figure 36 is the relatively intact profile for the red filter as compared to either the achromatic or blue. This trend is clearly evident in the mean thresholds for the
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<th>MEAN</th>
<th>S.D.</th>
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<th>S.D.</th>
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TABLE 15
MEAN AND STANDARD DEVIATIONS FOR THRESHOLD VALUES (APOSTILBS) BY ECCENTRICITY AND GROUP FOR THE ACHROMATIC FILTER

CLINICALLY DEFINITE

PROBABLE
**TABLE 16**

MEAN AND STANDARD DEVIATIONS FOR THRESHOLD VALUES (APOSTILBS) BY ECCENTRICITY AND GROUP FOR THE RED FILTER

| ECCENTRICITY | NORMALS | | | | | | |
|--------------|---------|---------|---------|---------|---------|---------|
|              | MEAN    | S.D     | MEAN    | S.D     | MEAN    | S.D     |
| Fovea        | 0.12    | 0.15    | 304.51  | 457.01  | 58.87   | 73.88   |
| Temporal     | 61.66   | 30.81   | 328.45  | 378.00  | 500.20  | 428.70  |
|              | 177.48  | 87.71   | 449.33  | 318.64  | 579.20  | 394.31  |
|              | 373.88  | 190.30  | 449.33  | 296.09  | 821.31  | 261.85  |
|              | 341.20  | 174.71  | 589.18  | 294.77  | 719.97  | 324.18  |
|              | 390.07  | 158.95  | 679.60  | 251.04  | 765.56  | 323.83  |
|              | 549.65  | 214.86  | 744.99  | 303.46  | 790.32  | 298.28  |
|              | 848.95  | 179.08  | 763.36  | 229.17  | 967.65  | 91.49   |

**NOTE:**

- The table above provides mean and standard deviation values for threshold values (in apostilbs) at different eccentricities for normals, clinically definite, and probable groups, and for the red filter.
- The eccentricities are measured from the fovea in both nasal and temporal directions.
- The mean values are given for each eccentricity level, with the standard deviations in parentheses.
- The data is organized in a tabular format, with columns for mean and standard deviation values for each group.
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TABLE 18

MEAN AND STANDARD DEVIATIONS FOR THRESHOLD VALUES (APOSTILBS) BY ECCENTRICITY AND GROUP FOR THE ACHROMATIC FILTER

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<td>386.03</td>
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<td>0</td>
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<td>497.95</td>
</tr>
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<td>303.36</td>
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<tr>
<td>70</td>
<td>878.72</td>
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</tr>
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<td>S.D</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>OPTIC NEURITIS</td>
<td>NO OPTIC NEURITIS</td>
</tr>
<tr>
<td>NASAL</td>
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<td>40</td>
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<td>305.35</td>
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<td>416.98</td>
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<td>297.07</td>
<td>434.44</td>
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<tr>
<td>Fovea</td>
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<tr>
<td>0</td>
<td>514.62</td>
<td>519.32</td>
</tr>
<tr>
<td>TEMPORAL</td>
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<td>5</td>
<td>296.37</td>
<td>435.01</td>
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<td>221.82</td>
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<td>340.41</td>
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<td>433.90</td>
<td>333.13</td>
</tr>
<tr>
<td>70</td>
<td>636.77</td>
<td>318.38</td>
</tr>
</tbody>
</table>
AT 45 APOTILB BACKGROUND
AND PROBABLE (PB) MS SUBJECTS FOR AN ACHROMATIC FILTER
SENSITIVITY GRADIENTS FOR NORMAL, CLINICALLY DEFINITE (CD),

Figure 30

ECCErTRICITY

Legend

NORMALS n=30

THRESHOLD: LOG APOTILBS
FIGURE 31

SENSITIVITY GRADIENTS FOR NORMAL, CLINICALLY DEFINITE (CD), AND PROBABLE (PB) MS SUBJECTS FOR A RED FILTER AT 45 APOSTILB BACKGROUND
FIGURE 32

SENSITIVITY GRADIENTS FOR NORMAL, CLINICALLY DEFINITE (CD), AND PROBABLE (PB) MS SUBJECTS FOR A BLUE FILTER AT 45 APOSTILB BACKGROUND
FIGURE 33

SENSITIVITY GRADIENTS FOR OPTIC NEURITIS (ON) AND NON-OPTIC NEURITIS (NON) SUBJECTS FOR AN ACHROMATIC FILTER AT 45 APOSTILB BACKGROUND
FIGURE 34

SENSITIVITY GRADIENTS FOR OPTIC NEURITIS (ON) AND NON-OPTIC NEURITIS (NON) SUBJECTS FOR A RED FILTER AT 45 APOSTILB BACKGROUND
FIGURE 35

SENSITIVITY GRADIENTS FOR OPTIC NEURITIS (ON) AND NON-OPTIC NEURITIS (NON) SUBJECTS FOR A BLUE FILTER AT 45 APOSTILB BACKGROUND
FIGURE 36
SENSITIVITY GRADIENTS FOR A MS PATIENT
SENSITIVITY GRADIENTS FOR A NORMAL SUBJECT

FIGURE 37

NORMAL MALE, AGE 23
various filters shown in Tables 15 to 17. All of the filters for the normals show a good progression of least sensitivity in the periphery to high sensitivity at the fovea. The thresholds for the probable MS patients also demonstrate a relatively consistent progression from low sensitivity in the periphery to high sensitivity at the fovea. This progression is more characteristic of the red than the achromatic and blue. As for the clinically definite MS patients, the mean thresholds have an irregular progression for the achromatic and blue. Again, the red for the clinically definite is relatively consistent in showing a regular progression of least sensitivity to high sensitivity.

Examination of Tables 18 to 20 reveals a similar pattern in that the mean thresholds for the red filter show a regular pattern of least sensitivity in the periphery to high sensitivity at the fovea. A poor progression in the thresholds are found among the optic neuritis MS patients for the achromatic and blue filters, unlike that for the non-optic neuritis patients.

As can be seen from Figures 30 to 35, the greatest difference between the normals and MS groups appears to be in the fovea and less so in the periphery. Foveal depression among the MS groups appears to occur more prominently with the blue and achromatic filters as compared to the red. The sensitivity gradients for the clinically definite and probable groups typically show a greater difference in the
foveal and adjacent regions as compared to the periphery. A similar trend is evident in the figures for MS patients with and without optic neuritis. Patients with optic neuritis tend to demonstrate a foveal depression for the blue and achromatic filters. Little difference between the two groups appears to be found in the periphery as compared to the center.

To determine if there was an overall significant difference between the three groups of normal, MS-clinically definite, and MS-probable, a repeated measures Multivariate Analysis of Variance (MANOVA)\(^1\) with one between factor (3 groups) and two within factors (3 filters and 14 eccentricities) was conducted. The 3x3x14 repeated MANOVA is a general case of the Split-Plot ANOVA design (Winer, 1971).

As shown in Table 21, there were many significant interactions and main effects in the data. Due to the lack of orthogonality (independence) between the variables, the actual interpretation of significant main effects becomes problematic. This is especially true with the group variable as almost all of the other variables interact significantly with it.

Nevertheless, the analysis revealed a significant main effect due to groups (F(2,49)=19.96, p<.0001). Tukey's Honestly Significant Differences (HSD) were calculated based upon the harmonic mean for subjects' of 13.06 and a critical difference value of 127.93.\(^2\) Using this critical value, the

\(^1\)All MANOVA's were performed using BMDP4V (Dixon, 1981).
\(^2\) Using a Bonferroni adjustment to correct for possssible
TABLE 21

MULTIVARIATE ANALYSIS OF VARIANCE BETWEEN NORMALS (n=30)
CLINICALLY DEFINITE (n=14), AND PROBABLE (n=8) MS
PATIENTS

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP (G)</td>
<td>51329111.04</td>
<td>2,49</td>
<td>25664555.52</td>
<td>19.96</td>
<td>.0000</td>
</tr>
<tr>
<td>FILTER (F)</td>
<td>11418434.62</td>
<td>2,98</td>
<td>5709217.31</td>
<td>86.86</td>
<td>.0000</td>
</tr>
<tr>
<td>ECCENTRICITY (E)</td>
<td>40283074.88</td>
<td>13,637</td>
<td>3098698.07</td>
<td>50.42</td>
<td>.0000</td>
</tr>
<tr>
<td>G X F</td>
<td>296655.38</td>
<td>2.79,68.45</td>
<td>74163.85</td>
<td>1.13</td>
<td>.3417*</td>
</tr>
<tr>
<td>G X E</td>
<td>3781798.22</td>
<td>7.15,175.17</td>
<td>145453.78</td>
<td>2.37</td>
<td>.0237*</td>
</tr>
<tr>
<td>F X E</td>
<td>4029295.62</td>
<td>11.72,574.19</td>
<td>154972.91</td>
<td>11.72</td>
<td>.0000*</td>
</tr>
<tr>
<td>G X F X E</td>
<td>2024808.96</td>
<td>23.44,574.19</td>
<td>38938.63</td>
<td>2.94</td>
<td>.0000*</td>
</tr>
</tbody>
</table>

Note: * Denotes probability after degrees of freedom have been adjusted by Greenhouse-Geisser.
overall mean thresholds for the normals (205.11 asb.) was found to be significantly different from the clinically definite (460.71 asb.) as well as the probable (583.79 asb.) MS groups at the .0001 level of significance. There was no significant difference between the mean thresholds for the clinically definite and probable groups. Tables 22 and 23 provide the means and absolute mean differences between the 3 groups. Thus, the Tukey's HSD indicates that the normals have significantly lower thresholds than the two MS groups, and that the two patient groups are similar with respect to their overall thresholds.

An overall significant difference was also found between filters \( F(2,98)=86.86, p<.01 \), eccentricity \( F(13,637)=50.42, p<.01 \) as well as the interactions between eccentricity x group \( F(7.15,175.17)=2.37, p<.02 \), filter x eccentricity \( F(11.72,574.19)=11.72, P<.01 \), and filter x eccentricity x group \( F(23.44,574.19)=2.94, p<.01 \).

Tukey's HSD were calculated for each filter against one another. Using a critical value of 122.97, the absolute "---

\( (cont'd) \) experiment-wise error due to the large number of mean comparisons, a critical value was computed for a probability level of .01/42. The actual critical value associated with a \( t \) value of .9999 was found through the U.B.C. Computing Centre fortran subroutine programme known as UBC Probability (1981).

\( ^1 \) When the orthogonal polynomials were found not to be independent or to have equal variances, indicating a problem of symmetry due to outliers or some carry over effect from one within factor level to the next, Greenhouse-Geisser adjustments were computed. The Greenhouse-Geisser is a conservative test for rejecting the null hypothesis by reducing the degrees of freedom through an epsilon (\( \epsilon \)) factor. By setting \( \epsilon \) to its lower bound, the Greenhouse-Geisser raises the critical value necessary for significance (Winer, 1962).
## Table 22

Mean Thresholds (Apostilbs) for Normals (n=30), Clinically Definite (n=14), and Probable (n=8) MS Patients Across Filters and Eccentricities

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>205.11</td>
</tr>
<tr>
<td>Clinically Definite</td>
<td>460.71</td>
</tr>
<tr>
<td>Probable</td>
<td>583.79</td>
</tr>
</tbody>
</table>
### TABLE 23

**ABSOLUTE MEAN THRESHOLD DIFFERENCE (APOSTILBS) FOR NORMALS (n=30) CLINICALLY DEFINITE (n=14), AND PROBABLE (n=8) MS PATIENTS ACROSS FILTERS AND ECCENTRICITIES**

<table>
<thead>
<tr>
<th>COMPARISON</th>
<th>MEAN DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL VS. PB</td>
<td>378.68 *</td>
</tr>
<tr>
<td>NORMAL VS. CD</td>
<td>255.60 *</td>
</tr>
<tr>
<td>PB VS. CD</td>
<td>123.08</td>
</tr>
</tbody>
</table>

**Note:** PB - PROBABLE  
CD - CLINICALLY DEFINITE  
* - SIGNIFICANT AT THE .0001 LEVEL
The difference (Table 24) between the mean of the achromatic filter (mean=268.06 asb.) and the red filter (453.33 asb.) was significantly different at the .0001 level. The absolute differences between the mean threshold value for the red and blue (275.15 asb.) filters were also significantly different. There was no significant difference between the achromatic and blue filters.

Thus, overall, the red filter had a significantly higher threshold than either the achromatic or blue. The lack of a significant difference between the achromatic and blue may have been due to the lack of blue in the red filter. The nonsignificant $F$ for the interaction between filter and group would suggest that the pattern of red > blue, red > achromatic, and blue = achromatic is consistent across the three groups.

The main effect of eccentricity ($F(13,637)=50.42$, $p<.01$) is a trivial one in that it only reflects a change in sensitivity across the fovea as does the significant interaction of filter x eccentricity ($F(11.72,574.19)=11.72$, $p<.01$). Table 25 provides the mean threshold values across the three filters for each of the 14 eccentricities. Tukey's HSD were calculated using a critical value of 118.69 for a significance level of .0001, and the resulting absolute mean differences are presented in Table 26. As can be seen from the table, the fovea (0°) is consistently significantly different from eccentricities past 10°. The 0° and the two 10° (nasal and temporal) eccentricities have the lowest mean
TABLE 24

ABSOLUTE MEAN THRESHOLD DIFFERENCE (APOSTILBS) FOR NORMALS (n=30) CLINICALLY DEFINITE (n=14), AND PROBABLE (n=8) MS PATIENTS BY FILTERS

<table>
<thead>
<tr>
<th>COMPARISON</th>
<th>MEAN DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED VS. ACHROMATIC</td>
<td>185.27*</td>
</tr>
<tr>
<td>RED VS. BLUE</td>
<td>178.28*</td>
</tr>
<tr>
<td>ACHROMATIC VS. BLUE</td>
<td>6.99</td>
</tr>
</tbody>
</table>

Note: * - SIGNIFICANT AT THE .0001 LEVEL
TABLE 25

MEAN THRESHOLDS (APOSTILBS) FOR ALL GROUPS AND FILTERS BY ECCENTRICITY

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAL</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>539.40</td>
</tr>
<tr>
<td>30</td>
<td>439.25</td>
</tr>
<tr>
<td>20</td>
<td>313.34</td>
</tr>
<tr>
<td>15</td>
<td>259.83</td>
</tr>
<tr>
<td>10</td>
<td>217.32</td>
</tr>
<tr>
<td>5</td>
<td>177.77</td>
</tr>
<tr>
<td>FOVEA</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>103.87</td>
</tr>
<tr>
<td>TEMPORAL</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>177.84</td>
</tr>
<tr>
<td>10</td>
<td>248.17</td>
</tr>
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</tr>
<tr>
<td>55</td>
<td>439.22</td>
</tr>
<tr>
<td>70</td>
<td>694.39</td>
</tr>
</tbody>
</table>
TABLE 26

ABSOLUTE MEAN THRESHOLD DIFFERENCE (APOSTILBS) BY ECCENTRICITY ACROSS GROUPS AND FILTERS

<table>
<thead>
<tr>
<th></th>
<th>NASAL</th>
<th>Fovea</th>
<th>Temporal</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>NASAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>100.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>226.06</td>
<td>125.91*</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>279.57</td>
<td>179.42*</td>
<td>53.51</td>
</tr>
<tr>
<td>15</td>
<td>322.08*</td>
<td>221.93*</td>
<td>96.02</td>
</tr>
<tr>
<td>10</td>
<td>361.63*</td>
<td>261.48*</td>
<td>135.57*</td>
</tr>
<tr>
<td>5</td>
<td>435.53*</td>
<td>335.38*</td>
<td>209.47*</td>
</tr>
<tr>
<td>Fovea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>361.56*</td>
<td>261.41*</td>
<td>135.50*</td>
</tr>
<tr>
<td>10</td>
<td>291.29*</td>
<td>191.08*</td>
<td>65.17</td>
</tr>
<tr>
<td>20</td>
<td>192.06*</td>
<td>91.91</td>
<td>34.00</td>
</tr>
<tr>
<td>30</td>
<td>208.44*</td>
<td>108.29*</td>
<td>17.62</td>
</tr>
<tr>
<td>40</td>
<td>177.53*</td>
<td>77.38</td>
<td>48.53</td>
</tr>
<tr>
<td>55</td>
<td>100.18</td>
<td>0.03</td>
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<tr>
<td>70</td>
<td>154.99*</td>
<td>255.14*</td>
<td>381.05*</td>
</tr>
</tbody>
</table>

NOTE: * - SIGNIFICANT AT THE .0001 LEVEL
threshold values compared with their periphery. Adjacent peripheral eccentricities tend not to be significantly different from each other except for the temporal 70° eccentricity, which is significantly different (higher threshold) than any other eccentricity.

To evaluate the significant interaction between filter and eccentricity ($F(11.72,574.19)=11.72$, $p<.0001$), Tukey's HSD were computed between the filters for each eccentricity across the 3 filters using the critical value of 118.69 ($p$ value of .0001). The resulting absolute mean differences between the 3 filters may be found in Table 27.

As stated earlier, the significant interaction between eccentricity and filter reflects the distribution of the cones and rods across the retina. The largest significant differences as calculated in Table 27 occur in the periphery (beginning from 20° temporally and 15° nasally) between the achromatic and red filters (higher thresholds for the red), followed by the differences between the red and blue (higher thresholds for the red). There were no significant mean differences between the blue and achromatic filters.

The pattern found in Table 27 typically demonstrates the lack of sensitivity in the periphery for the red, i.e. the red show a higher threshold in the periphery than the other filters. Though nonsignificant, the mean differences between the achromatic and blue reflect a similar trend as found in the red, i.e., the blue has a higher threshold in the peripheral eccentricities when compared to the
**TABLE 27**

**ABSOLUTE MEAN THRESHOLD (APOSTILBS) DIFFERENCE BETWEEN FILTERS BY ECCENTRICITY**

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>RED VS. ACHROMATIC</th>
<th>RED VS. BLUE</th>
<th>BLUE VS. ACHROMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>352.17*</td>
<td>342.58*</td>
<td>9.59</td>
</tr>
<tr>
<td>30</td>
<td>318.09*</td>
<td>288.37*</td>
<td>29.72</td>
</tr>
<tr>
<td>20</td>
<td>231.18*</td>
<td>221.60*</td>
<td>9.58</td>
</tr>
<tr>
<td>15</td>
<td>172.97*</td>
<td>184.64*</td>
<td>11.67</td>
</tr>
<tr>
<td>10</td>
<td>59.42</td>
<td>76.24</td>
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<td>29.56</td>
<td>57.56</td>
<td>28.00</td>
</tr>
<tr>
<td>FOVEA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19.50</td>
<td>15.47</td>
<td>4.03</td>
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<tr>
<td>TEMPORAL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>23.13</td>
<td>56.49</td>
<td>33.36</td>
</tr>
<tr>
<td>10</td>
<td>97.08</td>
<td>105.89</td>
<td>8.81</td>
</tr>
<tr>
<td>20</td>
<td>231.20*</td>
<td>251.68*</td>
<td>20.48</td>
</tr>
<tr>
<td>30</td>
<td>230.67*</td>
<td>248.99*</td>
<td>18.32</td>
</tr>
<tr>
<td>40</td>
<td>298.09*</td>
<td>265.18*</td>
<td>32.91</td>
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<td>55</td>
<td>353.20*</td>
<td>299.64*</td>
<td>53.56</td>
</tr>
<tr>
<td>70</td>
<td>317.64*</td>
<td>263.02*</td>
<td>54.62</td>
</tr>
</tbody>
</table>

**Note:** * - SIGNIFICANT AT THE .0001 LEVEL
achromatic. The increase in threshold for the red and blue as one moves away from the fovea is expected as the cone population reduces drastically when moving toward the periphery (Østerberg, 1935). The finding of red yielding a significantly higher threshold than an achromatic or blue stimulus has been confirmed with normal subjects by Lakowski and Dunn (1981).

In order to examine the significant interaction between eccentricity and group (F(7.15,175.17)=2.37, p<.02), Tukey's HSD were computed across filters using a critical value of 120.00. Table 28 provides the absolute mean differences between the 3 groups by eccentricity. The largest number of significant mean differences at the .0001 level were between the normal and probable groups. All eccentricities, except the fovea (0°), were significantly different. All eccentricities were significantly different between the normal and clinically definite groups. With respect to the comparison between the two MS groups, all eccentricities (excluding the 10° nasal and 55° temporal) were significantly different at the .0001 level. For all of the group comparisons, the nasal part of the field typically yielded greater mean differences than the temporal region.

Thus both MS groups have significantly higher thresholds than the normals across all eccentricities, except at the fovea between the probable and normal groups. The magnitude of this difference appears to be greater in the nasal field, suggesting a differential effect (due to
TABLE 28

ABSOLUTE MEAN THRESHOLD (APOSTILBS) DIFFERENCE BETWEEN GROUPS BY ECCENTRICITY

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>NORMAL VS. PB</th>
<th>NORMAL VS. CD</th>
<th>PB VS. CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAL 40</td>
<td>398.62*</td>
<td>263.88*</td>
<td>134.74*</td>
</tr>
<tr>
<td>30</td>
<td>446.37*</td>
<td>305.99*</td>
<td>140.38*</td>
</tr>
<tr>
<td>20</td>
<td>484.08*</td>
<td>311.06*</td>
<td>173.02*</td>
</tr>
<tr>
<td>15</td>
<td>419.78*</td>
<td>222.06*</td>
<td>197.72*</td>
</tr>
<tr>
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<td>377.79*</td>
<td>278.66*</td>
<td>99.13</td>
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<td>5</td>
<td>390.75*</td>
<td>245.03*</td>
<td>145.72*</td>
</tr>
<tr>
<td>Fovea 0</td>
<td>62.10</td>
<td>349.89*</td>
<td>287.79*</td>
</tr>
<tr>
<td>Temporal 5</td>
<td>392.42*</td>
<td>243.03*</td>
<td>149.39*</td>
</tr>
<tr>
<td>10</td>
<td>371.14*</td>
<td>236.56*</td>
<td>134.58*</td>
</tr>
<tr>
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<td>248.28*</td>
<td>243.99*</td>
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<td>221.15*</td>
<td>147.05*</td>
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<td>242.29*</td>
<td>176.74*</td>
</tr>
<tr>
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<td>352.04*</td>
<td>236.11*</td>
<td>115.93</td>
</tr>
<tr>
<td>70</td>
<td>326.83*</td>
<td>174.40*</td>
<td>152.43*</td>
</tr>
</tbody>
</table>

Note: PB - PROBABLE MS
CD - CLINICALLY DEFINITE MS
* - SIGNIFICANT AT THE .0001 LEVEL
the possible disease pathology) across the retina. As with
the normals, the probable and clinically definite groups
differ significantly at the fovea with the latter group
having significantly higher thresholds. A possible factor
contributing to the finding of a lack of significance at the
fovea between the normal and probable groups may be found in
the section entitled Optic Neuritis.

To examine the significant 3 way interaction between
group x filter x eccentricity \( (F(23.44,574.19)=2.94, \]
\[ p<.0001) \), Tukey's HSD were calculated for each eccentricity
by group and filter. The critical value used was 118.69
\( (.0001 \) level of probability). Tables 29, 30, and 31 provide
the absolute mean differences for the achromatic, red, and
blue filters respectively.

Examination of the tables reveals that the largest mean
differences tended to be between the normal and probable
groups across all eccentricities except at the fovea. All
eccentricities were significantly different between the
normal and clinically definite groups.

Although the red filter was significantly higher than
the blue or or achromatic filters (discussed earlier), the
blue filter had the greater number of large mean differences
\( (300 or above). Although this may not be significant, the
larger number of mean differences may indicate a greater
susceptability of the blue cones over the red. It is
interesting to note that the red has slighter larger mean
differences than the achromatic. Though any interpretation
TABLE 29

ABSOLUTE MEAN THRESHOLD (APOSTILBS) DIFFERENCE BETWEEN GROUPS BY ECCENTRICITY FOR THE ACHROMATIC FILTER

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
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<th>NORMAL VS. CD</th>
<th>PB VS. CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAL 40</td>
<td>413.32*</td>
<td>239.28*</td>
<td>174.04*</td>
</tr>
<tr>
<td>30</td>
<td>437.10*</td>
<td>303.26*</td>
<td>133.84*</td>
</tr>
<tr>
<td>20</td>
<td>398.51*</td>
<td>275.10*</td>
<td>123.41*</td>
</tr>
<tr>
<td>15</td>
<td>344.08*</td>
<td>203.66*</td>
<td>140.42*</td>
</tr>
<tr>
<td>10</td>
<td>359.59*</td>
<td>279.84*</td>
<td>79.75</td>
</tr>
<tr>
<td>5</td>
<td>373.55*</td>
<td>232.76*</td>
<td>140.79*</td>
</tr>
<tr>
<td>FOVEA 0</td>
<td>73.56</td>
<td>375.01*</td>
<td>301.45*</td>
</tr>
<tr>
<td>TEMPORAL 5</td>
<td>370.15*</td>
<td>240.81*</td>
<td>129.34*</td>
</tr>
<tr>
<td>10</td>
<td>378.80*</td>
<td>261.06*</td>
<td>117.74</td>
</tr>
<tr>
<td>20</td>
<td>445.18*</td>
<td>274.83*</td>
<td>170.35*</td>
</tr>
<tr>
<td>30</td>
<td>372.41*</td>
<td>141.32*</td>
<td>231.09*</td>
</tr>
<tr>
<td>40</td>
<td>403.37*</td>
<td>213.38*</td>
<td>189.99*</td>
</tr>
<tr>
<td>55</td>
<td>416.19*</td>
<td>236.03*</td>
<td>180.16*</td>
</tr>
<tr>
<td>70</td>
<td>472.08*</td>
<td>295.08*</td>
<td>177.00*</td>
</tr>
</tbody>
</table>

Note: PB - PROBABLE MS
CD - CLINICALLY DEFINITE MS
* - SIGNIFICANT AT THE .0001 LEVEL
TABLE 30

ABSOLUTE MEAN THRESHOLD (APOSTILBS) DIFFERENCE BETWEEN GROUPS BY ECCENTRICITY FOR THE RED FILTER

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>NORMAL VS. PB</th>
<th>NORMAL VS. CD</th>
<th>PB VS. CD</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>288.30*</td>
<td>202.23*</td>
<td>86.07</td>
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<tr>
<td>30</td>
<td>424.28*</td>
<td>309.81*</td>
<td>114.47</td>
</tr>
<tr>
<td>20</td>
<td>477.48*</td>
<td>437.53*</td>
<td>39.95</td>
</tr>
<tr>
<td>15</td>
<td>446.82*</td>
<td>312.40*</td>
<td>134.42*</td>
</tr>
<tr>
<td>10</td>
<td>413.30*</td>
<td>300.56*</td>
<td>112.74</td>
</tr>
<tr>
<td>5</td>
<td>425.76*</td>
<td>278.34*</td>
<td>147.42*</td>
</tr>
<tr>
<td>FOVEA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58.86</td>
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<td>245.64*</td>
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<tr>
<td>TEMPORAL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>438.54*</td>
<td>266.79*</td>
<td>171.75*</td>
</tr>
<tr>
<td>10</td>
<td>401.72*</td>
<td>271.85*</td>
<td>129.87*</td>
</tr>
<tr>
<td>20</td>
<td>447.42*</td>
<td>215.30*</td>
<td>232.14*</td>
</tr>
<tr>
<td>30</td>
<td>378.77*</td>
<td>338.40*</td>
<td>40.37</td>
</tr>
<tr>
<td>40</td>
<td>354.93*</td>
<td>375.48*</td>
<td>20.56</td>
</tr>
<tr>
<td>55</td>
<td>240.68*</td>
<td>213.71*</td>
<td>26.97</td>
</tr>
<tr>
<td>70</td>
<td>118.70*</td>
<td>246.50*</td>
<td>94.05</td>
</tr>
</tbody>
</table>

Note: PB - PROBABLE MS
CD - CLINICALLY DEFINITE MS
* - SIGNIFICANT AT THE .0001 LEVEL
### TABLE 31

**ABSOLUTE MEAN THRESHOLD (APOSTILBS) DIFFERENCE BETWEEN GROUPS BY ECCENTRICITY FOR THE BLUE FILTER**

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>NORMAL VS. PB</th>
<th>NORMAL VS. CD</th>
<th>PB VS. CD</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>494.24*</td>
<td>350.13*</td>
<td>144.12*</td>
</tr>
<tr>
<td>30</td>
<td>477.74*</td>
<td>304.91*</td>
<td>172.82*</td>
</tr>
<tr>
<td>20</td>
<td>576.26*</td>
<td>220.57*</td>
<td>355.68*</td>
</tr>
<tr>
<td>15</td>
<td>468.44*</td>
<td>150.10*</td>
<td>318.34*</td>
</tr>
<tr>
<td>10</td>
<td>360.47*</td>
<td>255.56*</td>
<td>104.91</td>
</tr>
<tr>
<td>5</td>
<td>372.93*</td>
<td>223.99*</td>
<td>148.94*</td>
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<tr>
<td>Fovea</td>
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<td></td>
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<tr>
<td>0</td>
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<td>370.29*</td>
<td>316.29*</td>
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<tr>
<td>TEMPORAL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>368.64*</td>
<td>221.51*</td>
<td>147.13*</td>
</tr>
<tr>
<td>10</td>
<td>332.92*</td>
<td>176.77*</td>
<td>156.15*</td>
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<td>584.20*</td>
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<td>329.49*</td>
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<td>354.44*</td>
<td>183.75*</td>
<td>169.69*</td>
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<tr>
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<td>478.22*</td>
<td>158.56*</td>
<td>319.66*</td>
</tr>
<tr>
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<td>399.25*</td>
<td>258.58*</td>
<td>140.67*</td>
</tr>
<tr>
<td>70</td>
<td>390.53*</td>
<td>203.45*</td>
<td>187.07*</td>
</tr>
</tbody>
</table>

**Note:** PB - PROBABLE MS  
CD - CLINICALLY DEFINITE MS  
* - SIGNIFICANT AT THE .0001 LEVEL
of this difference is rather questionable, it would be
tempting to speculate that the finding of greater mean
differences among the blue and red filters as compared to
the achromatic resulted from the sensitivity of the cone
system over the rod to the effects of MS.

The nasal eccentricities typically revealed greater
mean threshold differences than the temporal for all group
comparisons for each filter. This trend may possibly be
indicative of some selective pathological process occurring
in the eyes of the MS patients.

At 30° eccentricity, the thresholds for virtually all
of the comparisons becomes much lower than the 20°
eccentricity. From Tables 15 to 17, which contained the
standard deviations for each group by filter and
eccentricity, variability in retinal thresholds as a result
of eccentricity indicates the following:

1. Among the normals, threshold variability increases with
eccentricity except at 20° and 30° temporally. Irregular
increases may also be seen at and past 30° eccentricity
for the achromatic filter only. The increase in
variability among normals is in agreement with previous
investigations (eg. Aulhorn & Harms, 1972; Lakowski &

2. For the clinically definite group, the variability in
thresholds is highest at the fovea. The remaining
eccentricities also demonstrate great variability across
the 3 filters, especially near the fovea.
3. For the probable group, higher variability in the thresholds tends to occur near the periphery but not at the fovea itself.

The drop in variability at 20° temporal and 30° nasal eccentricity is interesting in that one would have expected the reverse to have been true. Greater variability should have occurred at 20° temporal eccentricity resulting from its proximity to the blind spot. Similar findings regarding the drop in variability in the periphery has been reported by Dunn (1981) for 40° nasal and 30° temporal eccentricity under photopic conditions.

a. Fovea

To examine more closely the involvement of the fovea with respect to the other eccentricities, Pearson Product-Moment correlations were computed for the foveal threshold against the other eccentricities.\(^1\) Table 32 provides the correlations\(^2\) for the normal, clinically definite, and probable groups for the achromatic filter. Tables 33 and 34 provide similar results for the red and blue filters respectively. Correlations for the normal group tended to be nonsignificant with the fovea. The direction of the correlation typically became negative after 5° for the red and at 5° for the blue and achromatic. This functional pattern reflects the

---

\(^1\) The correlations were computed using the Statistical Package for the Social Sciences, version X (1983).

\(^2\) Significance is based upon a two-tailed test.
<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>NORMALS</th>
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<th>CLINICALLY DEFINITE</th>
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<td>.03</td>
<td>.47</td>
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<td>.71**</td>
</tr>
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<td>.68**</td>
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<td>.69**</td>
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<td>.50</td>
<td>.72**</td>
</tr>
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<td>.08</td>
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<td>.58</td>
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Note: * - .05 LEVEL OF SIGNIFICANCE  
** - .01 LEVEL OF SIGNIFICANCE
TABLE 33
CORRELATIONS BETWEEN THE Fovea AND ECCENTRICITIES
BY GROUP FOR THE RED FILTER

<table>
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<th>CLINICALLY DEFINITE</th>
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Note: * -.05 LEVEL OF SIGNIFICANCE
       ** -.01 LEVEL OF SIGNIFICANCE
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<td>.41</td>
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<tr>
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<td>-.11</td>
<td>.64</td>
<td>.72**</td>
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</tr>
<tr>
<td>TEMPORAL</td>
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<td></td>
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<td></td>
</tr>
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<td>.64</td>
<td>.73**</td>
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<tr>
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<tr>
<td>70</td>
<td>.39*</td>
<td>.26</td>
<td>.27</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: * - .05 LEVEL OF SIGNIFICANCE
** - .01 LEVEL OF SIGNIFICANCE
distribution of cones and rods in the retina, indicating the existence of two different systems as has been demonstrated by numerous researchers.

With respect to the clinically definite and probable groups, the correlations between the foveal threshold and other eccentricities were positive. The only exception to this trend was between 30° and 55° temporally for the probable subjects. The majority of the correlations for the clinically definite group were significant.

To examine more rigorously the possible differences in the correlations between the various filters and groups, the correlations were transformed into $Z'$. Standard error of the differences were computed for each filter by group. The normal curve was then examined to determine if the differences between the $Z'$ were statistically significant.

Results of the analysis revealed that the blue filter for both the clinically definite and probable MS patients had significantly more ($>.01$) large positive correlations than did either the achromatic or red. Moreover, the achromatic had significantly more positive correlations than the red at the .01 level of significance. For the normals, only the red demonstrated significantly larger negative correlations. This confirms the descriptive observations noted earlier.
b. Optic Neuritis

To examine the possible role that optic neuritis (ON) may have had on the threshold results from the MS patients, the data was reanalyzed. A repeated measures MANOVA for 1 between group factor (MS-ON, MS-no ON) and 2 within factors (3 filters, 14 eccentricities) was done.¹

The results of the analysis are presented in Table 35. There was no significant main effect for groups (F(1, 20)=0.13, p >.05), nor for filter x group (F(1.36,27.23)=2.69, p >.05), nor eccentricity x group (F(3.09,61.85)=2.19, p >.05). The filter x eccentricity x group interaction was also nonsignificant (F(8.04,160.31)=1.21, p >.05).

A significant main effect was obtained for filter (F(2,40)=42.73, p<.01). Using a critical value of 166.51, Tukey's HSD were computed between the mean thresholds for the achromatic (443.97 asb.), red (632.66 asb.), and blue filters (453.83). The absolute mean differences (Table 36) between the red and the blue and achromatic filters respectively were both significant at the .0001 level. The mean difference between the blue and red filters were not significant. These findings are identical to that reported in the main study, indicating

¹An analysis including the normal group was also done. As the results were similar to the one reported in the main study, it was not discussed. The MANOVA results for this analysis may be found in Appendix G.
<table>
<thead>
<tr>
<th>SOURCE</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP (G)</td>
<td>421653.76</td>
<td>1,20</td>
<td>421653.76</td>
<td>0.13</td>
<td>.7199</td>
</tr>
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<td>FILTER (F)</td>
<td>7353989.75</td>
<td>2,40</td>
<td>3676994.87</td>
<td>42.73</td>
<td>.0000</td>
</tr>
<tr>
<td>ECCENTRICITY (E)</td>
<td>16685914.32</td>
<td>13.09,61.85</td>
<td>1283531.87</td>
<td>10.94</td>
<td>.0000*</td>
</tr>
<tr>
<td>G X F</td>
<td>463532.58</td>
<td>1.36,27.23</td>
<td>231766.29</td>
<td>2.69</td>
<td>.0799*</td>
</tr>
<tr>
<td>G X E</td>
<td>3344496.91</td>
<td>3.09,61.85</td>
<td>257268.99</td>
<td>2.19</td>
<td>.0960*</td>
</tr>
<tr>
<td>F X E</td>
<td>2808966.91</td>
<td>8.04,160.31</td>
<td>108037.19</td>
<td>6.42</td>
<td>.0000*</td>
</tr>
<tr>
<td>G X F X E</td>
<td>530210.39</td>
<td>8.04,160.31</td>
<td>20392.71</td>
<td>1.21</td>
<td>.2954*</td>
</tr>
</tbody>
</table>

NOTE: * Denotes probability after degrees of freedom were adjusted by the Greenhouse-Geisser.
TABLE 36

ABSOLUTE MEAN THRESHOLD DIFFERENCE (APOSTILBS) FOR OPTIC NEURITIS AND NON OPTIC NEURITIS MS PATIENTS BY FILTER

<table>
<thead>
<tr>
<th>COMPARISON</th>
<th>MEAN DIFFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED VS. ACHROMATIC</td>
<td>188.69*</td>
</tr>
<tr>
<td>RED VS. BLUE</td>
<td>178.83*</td>
</tr>
<tr>
<td>ACHROMATIC VS. BLUE</td>
<td>9.86</td>
</tr>
</tbody>
</table>

NOTE: * - SIGNIFICANT AT THE .0001 LEVEL
that the thresholds were higher for the red filter over the achromatic and blue. Although the mean threshold for the blue was slightly higher than that of the achromatic, the difference was not significant. The lack of significance was seen as resulting from the large contribution of blue energy in white (achromatic) light.

There was a significant main effect for eccentricity ($F(3.09, 61.85) = 10.94, p < .01$). As in the main study, the significant effect for eccentricity was seen as resulting from differential sensitivity across the retina. Threshold values were the lowest at the fovea ($0^\circ$) and increased in the periphery. Table 37 provides the mean threshold values for the eccentricities averaged across the 3 filters.

Tukey's HSD were calculated using a critical value of 153.43 and the absolute mean differences are shown in Table 38. Again as in the main results, the greatest significant differences (at the .0001 level) were between the periphery and central areas of the fovea. The greatest differences tended to be found when comparing the fovea.

A significant interaction was found for filter x eccentricity ($F(8.04, 160.31) = 6.42, p < .01$). Table 39 provides the mean threshold values for each of the 3 filters. Tukey's HSD, using a critical value of 152.34, were computed. Table 40 shows the absolute mean differences between the filters by eccentricities.
TABLE 37

MEAN THRESHOLDS (APOSTILBS) FOR OPTIC NEURITIS AND NON OPTIC NEURITIS PATIENTS ACROSS FILTERS BY ECCENTRICITY

<table>
<thead>
<tr>
<th>ECCENTRICITY</th>
<th>MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASAL</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>717.55</td>
</tr>
<tr>
<td>30</td>
<td>645.16</td>
</tr>
<tr>
<td>20</td>
<td>542.13</td>
</tr>
<tr>
<td>15</td>
<td>444.15</td>
</tr>
<tr>
<td>10</td>
<td>413.16</td>
</tr>
<tr>
<td>5</td>
<td>362.77</td>
</tr>
<tr>
<td>FOVEA</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>255.38</td>
</tr>
<tr>
<td>TEMPORAL</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>361.07</td>
</tr>
<tr>
<td>10</td>
<td>425.50</td>
</tr>
<tr>
<td>20</td>
<td>559.62</td>
</tr>
<tr>
<td>30</td>
<td>488.63</td>
</tr>
<tr>
<td>40</td>
<td>527.57</td>
</tr>
<tr>
<td>55</td>
<td>580.69</td>
</tr>
<tr>
<td>70</td>
<td>818.74</td>
</tr>
</tbody>
</table>
**TABLE 38**

**ABSOLUTE MEAN THRESHOLD DIFFERENCE (APOSTILBS) BY ECCENTRICITY ACROSS OPTIC NEURITIS PATIENTS AND NON OPTIC NEURITIS PATIENTS AND FILTERS**

<table>
<thead>
<tr>
<th></th>
<th>NASAL</th>
<th>Fovea</th>
<th>TEMPORAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>NASAL</td>
<td>40</td>
<td>72.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td></td>
<td>175.42*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>273.40*</td>
<td>201.01*</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>304.39*</td>
<td>128.97</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>354.78*</td>
<td>179.36*</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>462.17*</td>
<td>389.78*</td>
</tr>
<tr>
<td>FOVEA</td>
<td>0</td>
<td>286.75*</td>
<td>188.77*</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>292.05*</td>
<td>116.63</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>157.93*</td>
<td>219.66*</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>228.92*</td>
<td>156.53*</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>189.98*</td>
<td>117.59</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>136.86</td>
<td>64.47</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>101.19</td>
<td>173.58*</td>
</tr>
<tr>
<td>TEMPORAL</td>
<td>5</td>
<td>181.06*</td>
<td>83.08</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>292.05*</td>
<td>116.63</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>157.93*</td>
<td>219.66*</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>228.92*</td>
<td>156.53*</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>189.98*</td>
<td>117.59</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>136.86</td>
<td>64.47</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>101.19</td>
<td>173.58*</td>
</tr>
</tbody>
</table>

**NOTE:** * - SIGNIFICANT AT THE .0001 LEVEL
### Table 39

**Mean Thresholds (Apostilbs) for Optic Neuritis and Non Optic Neuritis Patients by Filters and Eccentricity**

<table>
<thead>
<tr>
<th>Eccentricity</th>
<th>Achromatic</th>
<th>Red</th>
<th>Blue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>591.21</td>
<td>887.84</td>
<td>673.61</td>
</tr>
<tr>
<td>30</td>
<td>523.49</td>
<td>832.58</td>
<td>579.39</td>
</tr>
<tr>
<td>20</td>
<td>429.64</td>
<td>737.49</td>
<td>459.28</td>
</tr>
<tr>
<td>15</td>
<td>365.78</td>
<td>600.12</td>
<td>366.55</td>
</tr>
<tr>
<td>10</td>
<td>394.86</td>
<td>471.85</td>
<td>372.77</td>
</tr>
<tr>
<td>5</td>
<td>353.77</td>
<td>410.18</td>
<td>324.36</td>
</tr>
<tr>
<td>Fovea</td>
<td>275.89</td>
<td>224.07</td>
<td>266.17</td>
</tr>
<tr>
<td>Temporal</td>
<td>357.49</td>
<td>405.40</td>
<td>320.31</td>
</tr>
<tr>
<td>5</td>
<td>408.65</td>
<td>509.35</td>
<td>358.51</td>
</tr>
<tr>
<td>10</td>
<td>489.99</td>
<td>692.14</td>
<td>496.74</td>
</tr>
<tr>
<td>20</td>
<td>394.99</td>
<td>679.73</td>
<td>391.17</td>
</tr>
<tr>
<td>30</td>
<td>402.47</td>
<td>740.69</td>
<td>439.56</td>
</tr>
<tr>
<td>40</td>
<td>456.75</td>
<td>762.36</td>
<td>522.97</td>
</tr>
<tr>
<td>55</td>
<td>770.55</td>
<td>903.41</td>
<td>782.25</td>
</tr>
<tr>
<td>ECCENTRICITY</td>
<td>RED VS. ACHROMATIC</td>
<td>RED VS. BLUE</td>
<td>BLUE VS. ACHROMATIC</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>NASAL 40</td>
<td>296.63*</td>
<td>214.23*</td>
<td>82.40</td>
</tr>
<tr>
<td>30</td>
<td>309.09*</td>
<td>253.19*</td>
<td>55.90</td>
</tr>
<tr>
<td>20</td>
<td>307.85*</td>
<td>278.21*</td>
<td>29.64</td>
</tr>
<tr>
<td>15</td>
<td>234.34*</td>
<td>233.57*</td>
<td>0.77</td>
</tr>
<tr>
<td>10</td>
<td>76.99</td>
<td>99.00</td>
<td>22.09</td>
</tr>
<tr>
<td>5</td>
<td>56.41</td>
<td>85.82</td>
<td>29.41</td>
</tr>
<tr>
<td>FOVEA 0</td>
<td>51.82</td>
<td>42.10</td>
<td>9.72</td>
</tr>
<tr>
<td>TEMPORAL 5</td>
<td>47.91</td>
<td>85.09</td>
<td>37.18</td>
</tr>
<tr>
<td>10</td>
<td>100.70</td>
<td>150.84</td>
<td>50.14</td>
</tr>
<tr>
<td>20</td>
<td>202.15*</td>
<td>195.40*</td>
<td>6.75</td>
</tr>
<tr>
<td>30</td>
<td>284.74*</td>
<td>288.56*</td>
<td>3.82</td>
</tr>
<tr>
<td>40</td>
<td>338.22*</td>
<td>301.13*</td>
<td>37.09</td>
</tr>
<tr>
<td>55</td>
<td>305.61*</td>
<td>239.39*</td>
<td>66.22</td>
</tr>
<tr>
<td>70</td>
<td>132.86*</td>
<td>121.16</td>
<td>11.70</td>
</tr>
</tbody>
</table>

NOTE: * - SIGNIFICANT AT THE .0001 LEVEL
The largest number of significant differences (at the .0001 level) are found between the red and achromatic filters, followed by the red and blue. There were no significant differences between the achromatic and blue filters.

As with the significant eccentricity x filter interaction found in the main study, the significant differences tends to begin at and past 10° nasally and temporarily. This trend is seen as resulting from the differential sensitivity of the retina to the red versus blue and achromatic filters. Again, the lack of significance between the achromatic and blue was seen as resulting from the presence of short wavelength light in white light.

c. Discriminant Analysis

To examine how accurately the normals and MS patients could be classified by the thresholds, a stepwise discriminant analysis was done for the three filters. Both the thresholds for the nasal and temporal peripheries were collapsed into a mean threshold for each inorder to protect the degrees of freedom. Thus three discriminant analyses using three measures of thresholds (fovea, nasal, and periphery) were conducted separately for the achromatic, red, and blue filters. The results of the analysis are shown in Table 41.
<table>
<thead>
<tr>
<th>GROUP</th>
<th>PREDICTED GROUP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL (n=30)</td>
<td>NORMAL</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>52.4%</td>
<td>47.6%</td>
</tr>
</tbody>
</table>

OVERALL CORRECT CLASSIFICATION = 78.43%

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PREDICTED GROUP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL (n=30)</td>
<td>NORMAL</td>
<td>96.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>28.6%</td>
<td>71.4%</td>
</tr>
</tbody>
</table>

OVERALL CORRECT CLASSIFICATION = 86.27%

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PREDICTED GROUP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL (n=30)</td>
<td>NORMAL</td>
<td>96.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>47.6%</td>
<td>52.4%</td>
</tr>
</tbody>
</table>

OVERALL CORRECT CLASSIFICATION = 78.43%
In terms of overall classification, the red filter correctly classified 86.27% of the normals and MS patients as compared to 78.43% for both the blue and achromatic. Both of these rates are far above that expected by chance.

The red filter correctly classified 96.7% of the normals and 71.4% of the MS patients. Only 28.6% of the patients were incorrectly classified as normals whereas 3.3% of the normals were incorrectly identified as belonging to the MS group. With respect to the achromatic and blue filters, more of the MS patients were classified as normal (52.4% and 47.6% respectively). The MS patients incorrectly identified were the probable patients. That is, the probable patients tended to be misclassified as normals.

In terms of overall group prediction as well as low false positives for not having MS, the red filter appears to provide the best results.

d. Threshold Classification

In order to provide a threshold level that would clinically identify an abnormal threshold from a normal one, log differences between the fovea and 30° nasal eccentricity were computed. Both the probable and clinically definite patients were collapsed into one group as the question centered upon which threshold would differentiate between MS and normals.
The log differences were then used to compute cumulative frequencies in an ascending manner for the normals and descending for the MS patients. The threshold at which most of the MS patients and normals could be discriminated from one another was found. This was done for each of the three filters separately.

For the achromatic filter, a log apostilb difference cut-off value of -2.60 correctly identified all of the MS patients and all but one of the normals. Similarly, the log apostilb difference value of -2.45 for the blue identified all but one of the MS patients as being different from the normals. No normal was identified as having an abnormal threshold using the value of -2.45.

With respect to the red filter, a log apostilb threshold value of -2.25 correctly separated all of the normals from all but one of the MS patients.
V. DISCUSSION

The results of the analysis supported the hypothesis that there would be a difference between the MS patients and normals with respect to their relative thresholds for a red, blue, and achromatic filter. MS patients have significantly higher thresholds across all eccentricities when compared to age-matched normals. Although the thresholds for the red are significantly greater than either the blue or achromatic filters, there is no overall group difference by filter. This would argue that the functional loss in cone/rod functioning is so great among the MS patients, at their present state in the disease, that all of the filters were affected. Such a conclusion needs to be guarded in that the magnitude of the difference between the 3 filters (across all groups) needs to be reassessed once the actual photometric measures for stimulus intensity is achieved. Until then, assuming that Synemed® is correct in stating that the F225 filters are photometrically equated, the relative difference between the filters reported here are valid. Support for the relative position of the red threshold for normals comes from Lakowski and Dunn (1981) who reported that the red (λD 532 nm.) yielded a "gradient from 1 and 1/2 to 2 log units below the others [achromatic, blue, and green]" (p. 195). Similar results were reported by Aulhorn and Harms (1972).
However, as pointed out by Lakowski and Dunn, the relative threshold gradients are highly dependent upon the background bowl adaptation level. Thus Lakowski and Dunn reported that under fully photopic conditions (250 cd/m²) the separation between the various filters become very small except at the fovea.

The significant interaction between group x filter x eccentricity revealed that:

1. MS-probable patients had significantly higher thresholds than normals across all eccentricities except the fovea,
2. MS-clinically definite patients had significantly higher thresholds across all eccentricities including the fovea, for the blue and achromatic filters only. For the red, significant mean thresholds were found only in the center from 20° temporally to 15° nasally. As with the normals, the greatest mean difference between the clinically definite and probable patients tended to occur at the fovea. Thus the clinically definite patients had significantly higher thresholds in the fovea when compared to the normals or MS-probable patients.
3. Losses in the field tended to be greater in the nasal rather than temporal regions, with the blue showing slightly more significant mean differences between the various groups than the red.

The differences in retinal sensitivity found in the MS groups is in agreement with the few studies that have been
done using static threshold perimetry. Serra and Mascia reported the presence of a small relative scotoma in the fovea of MS patients using an achromatic stimulus. The presence of a central defect and small scotoma 10°-20° temporally through static perimetry has also been reported by Van Dalen, Spekreyse and Greve (1981). The results from the present study are in agreement with these findings. Losses tend to be great at the fovea as well as at eccentricities adjacent to the fovea. However, the findings differ from the others in that the loss in MS appears to occur across all eccentricities except in the fovea of probable patients. A possible explanation for this will be discussed shortly.

Suprathreshold studies typically have revealed the presence of abnormal fields such as arcuate scotoma (Patterson and Heron, 1980), central and paracentral defects (Paton, 1924; Scott, 1957; Keltner, Johnson & Balestrery, 1979), and small scotoma in the periphery between 15° and 30° eccentricity (Meienberg, Flammer & Hans-Peter, 1982).

Again, the findings of the present study tend to agree with those from the suprathreshold studies in showing a loss in the visual field. It differs in that the loss occurs across the field, with the fovea showing identifiable losses. Moreover, the loss found in the present study is much more pronounced for the chromatic filters. As perimetric studies have focused upon the standard use of achromatic stimuli (due to instrumental difficulties in
presenting chromatic stimuli) the involvement of the cone system in MS has not been appreciated. Thus Meienberg et al. (1982), in using achromatic stimuli in standard suprathreshold testing, state that abnormality in MS is better detected with VEP since the defects found through the Octopus Automated Perimeter are not in the center but periphery. By not differentiating retinal receptor functioning (rod/cone), however, important information regarding basic as well as pathological functioning is lost. Understanding the involvement of the 2 retinal systems has considerable theoretical implications regarding symptomatology such as the fluctuation in visual acuity or glare reported by patients.

The results from the present study do differ from those conducted by Younge (1985) on an automated perimeter: the Octopus. Younge reported that the mean thresholds for MS patients overlapped with the mean thresholds for normals despite the fact that individual threshold values were lower for the MS patients. He concluded that the reason for the overlap was due to no cases of subacute optic nerve involvement. The present study, however has shown significant mean differences in the thresholds of MS patients from normals, both among patients with and without optic neuritis. The reason for the differences in the two studies centers upon the psychophysical conditions of the testing situation. In Younge's study, patients were tested with an achromatic stimulus at mesopic levels. In the
present study, however, the subjects were examined with chromatic filters, one more suited for assessing cone function. One serious drawback in the present study that limits any comparison with studies such as Younge is the difference in the psychophysical function of the instrument itself. The difference, discussed in the section on Methodological and Instrumental Problems, makes it extremely difficult to try and compare the present results with any other perimetric finding in MS. This, the problem of difference in instrumentation, is a serious problem in perimetry in general.

The results of the present study also differ from previous perimetric studies with respect to the observed fluctuations in the sensitivity progression from least in the periphery to the highest in the fovea. As stated earlier, perimetric research on MS has typically revealed the presence of irregular thresholds across the eccentricities, resulting in the profile known clinically as the swiss cheese field. Results of the present study indicates that this threshold variability is only found with blue and achromatic filters. The profile for the red filter is consistently good, with the sensitivity gradient increasing as one moves toward the fovea. It would be incorrect, therefore, to state that MS is characterized by swiss cheese fields. This is only true for achromatic (typically used) and blue stimuli. A red stimulus provides an entirely different perimetric profile, one peculiar to
the red cone involvement in MS.

The involvement of the cone system in MS can be seen in the correlation between the fovea and other eccentricities. For the normals, the correlations between the fovea and remaining eccentricities were nonsignificant and generally negative. Though nonsignificant, the negative direction could indicate the difference in cone functioning at the fovea and cone/rod functioning in the periphery. An interesting finding with the normals is the presence of positive correlations, again nonsignificant except for 70° temporal eccentricity for the blue filter, are found in the far nasal and temporal peripheries for the red and blue filters. This would seem to argue for a functional similarity between the fovea and far periphery, possibly due to the presence of cones in the periphery (e.g. Curcio, 1985).

The involvement of the cone system in MS reveals itself dramatically in the correlations between the fovea and remaining eccentricities. Both in the clinically definite and probable MS groups, the correlations with the fovea are generally significant and positive.

The pattern of the correlations among the two MS groups appears to result from extensive damage to the cone system, making it functionally indistinct from the rod system. This is supported by the fact that the largest positive correlations are found among the blue and achromatic filters. Unfortunately, there are no published studies on
dark adaptation and the effects of MS.

Among the normals, the correlations for the red and blue filters tend to be higher in a negative direction than for the achromatic, albeit nonsignificant. The dramatic change for the blue filter among the MS subjects to become highly positive with the other eccentricities suggests that the blue cone system may have become more functionally affected. As the correlations for the red filter for the 2 patient groups show fewer significant correlations than do the blue and achromatic, one might argue that the red cones are more resistant and tend to be the last of the cone system to be affected.

Although intriguing in that the results from the correlations would argue that the blue cones are more sensitive to the pathological effects of MS, it needs to be pointed out that this interpretation is highly dependent upon the adaptation level and filter characteristics. As the adaptation level is increased, the correlation between the fovea and periphery will decrease. Since it is assumed that the normals had no pathological condition affecting their retinal functioning, the lack of a significant correlation (be it positive or negative) is not surprising considering that the background bowl luminance was at the lower end of the photopic range (45 asb.). If the adaptation level was lowered, one would have expected to have found significant correlations (hopefully negative) between the fovea and periphery.
This interpretation regarding the role of adaptation has theoretical implications for the MS groups. As the correlations between the fovea and periphery for both patients became significantly positive, one might be able to argue that the correlations were due to a functional change in the cone system resulting from a change in the adaptational state of the MS eye, one which may fluctuate over time. This fluctation may result from conduction losses observed by other researchers in MS.

The one problematic finding in the present study is the lack of a significant difference at the fovea between the normal and probable MS groups. This is unexpected as one would have expected the fovea to demonstrate a difference between the two groups. Although there was a greater number of MS patients who did not have optic neuritis as compared to the clinically definite (whose foveal thresholds were significantly different from both the normals and probable), optic neuritis does not appear to play a role in that there was no significant difference in the thresholds between those patients with or without optic neuritis.

A possible interpretation of the lack of a significant difference at the fovea between the probable and normal groups is as follows. In the initial stages of the disease, the effects of demyelination occurs just outside the 0° eccentricity. This is supported by the earlier perimetric results of accurate scotoma or losses in the near periphery. However, as the disease progresses, to the point where a
patient is clearly identified as being clinically definite, the losses have extended into the 0° eccentricity. Thus although the cone system may be involved earlier in MS, the fovea itself may be relatively spared until the latter stages of the disease. Theoretical support for this may come from the research on spatial frequencies and the distribution of retinal ganglion cells.

MS has been reported to affect the intermediate and low spatial frequencies more so than the high frequencies (eg. Regan, Silver & Murray, 1972; Bodis-Wollner, Hendley, Mylin & Thornton, 1979; Regan, Raymond, Ginsberg & Murray, 1981). The robustness of the higher spatial frequencies may result from the distribution of the 3 retinal ganglion cells x, y, and w. According to Lennie (1980) and Stone, Dreher & Leventhal (1980), the w retinal ganglion cells are maximally distributed in and near the fovea and are felt to be responsible for spatial discrimination. As this would imply that input to these cells may come from the cone system, the robustness may be explained by the fact that high spatial resolution would require extensive cone damage before any loss is found at that frequency. Ideally, based upon the present correlational finding that the red exhibited less large mean differences than the blue, one would hope that the high spatial resolution (fine acuity) was a function of the red cone system as it is typically the last to be affected in diseases (eg. Birch, Chisholm, Kinnear, Marre’, Pinckers, Porkorny, Smith & Verriest, 1979). Thus if the red
cone system was responsible for the resolution of high spatial frequencies, the higher frequencies tend to be spared because of the resilience of the red cones to the pathological processes. Although this entire line of argument assumes that spatial frequencies are not the result of cortical functioning, it derives some support from the finding that the blue cone system can not mediate high spatial frequencies unlike the red (Boynton, 1979).

With respect to the significant interactions between eccentricity as well as between eccentricity and filter indicated that the retina has a differential sensitivity across its receptor distribution (rod/cone). Greater mean significant differences occurred between the periphery and the fovea. Significant differences also occurred between the central region and the periphery. Examination of the mean thresholds indicate that the fovea has the lowest threshold (highest sensitivity), followed by the central region. The thresholds increase when moving towards the periphery.

In addition, there is a selective difference between filter and eccentricity, with the largest significant mean differences found between the red and blue as well as red and achromatic. The significant differences tended to begin

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1 The importance of the cone system in spatial contrast sensitivity with respect to their distribution across the retina may explain why the upper hemiretina is more sensitive to spatial frequencies than the lower (Skrandies, 1985). According to a recent study by Curcio (1985), there is a higher proportion of rods in the lower retina. In either some inhibitory role or just due to their lack of sensitivity, the rods may actually decrease the sensitivity of the lower hemiretina to spatial frequencies.
past 15° nasal and 20° eccentricity. There was no significant mean differences between the achromatic and blue.

In all, the significant interactions between eccentricity and eccentricity and filter reflect a functional relationship based upon cone/rod distribution. It has generally been accepted since Østerberg (1935) that the cone population is at its greatest at 0° eccentricity and falls rapidly into the periphery. The inverse is felt to be true with the rods, none at 0° eccentricity and progressively increasing as moving into the periphery. Maximum rod density is traditionally felt to be at about 20° eccentricity. The results obtained tend to agree functionally with this distribution. Highest sensitivity for the filters is found in the periphery. Moving into the periphery, higher thresholds are found for the red as compared to the achromatic or blue. This is felt as being the result of fewer cones in the periphery of the retina, resulting in the need for greater intensity in detecting the red. The lack of a significant mean difference between the achromatic and blue is problematic in that the distribution of cones should have resulted in a functional pattern similar to the red, as has been found by others (eg. Verriest & Israel, 1965, Lakowski & Dunn, 1981). The reason for this negative finding is that the achromatic stimulus used in the F225 contains blue and that the similarity in wavelengths between the 2 resulted in nonsignificant threshold differences. However, by increasing the background
adaptation level to fully photopic (250 cd/m\(^2\)) a separation between the achromatic and blue filters should be achieved.

a. Theoretical Mechanism

As noted by Drance (1985a, 1985b), loss in foveal functioning tends to occur prior to the clinical detection of visual field defects. Thus Lakowski has argued and demonstrated through a variety of psychophysical techniques that colour vision losses, mediated through the cones, can occur in a wide variety of diseases before the onset of recognized visual defects (e.g. Lakowski, Bryett & Drance, 1972; Lakowski & Begg, 1976; Lakowski & Drance, 1978; Lakowski, Drance & Carsh, 1980).

The present study is in agreement with the finding on cone sensitivity, as is evident from the correlations between the fovea and remaining eccentricities for the 3 groups (normal, MS-clinically definite, MS-probable). According to the correlations, the generalized loss at the fovea and adjacent eccentricities would argue the presence of functional damage to the cone system as well as the rod. The functional loss among the cones, one which appears to be slightly greater for the blue, makes it difficult to differentiate between the rods and cones (interpreted from the positive correlations). That is, demyelination has disrupted the normal functional difference between the rod and cone systems.
Unfortunately, what has not been established by the present study is which of the two receptor systems is affected earlier. Because of the loss at the fovea, it is assumed by the author that the cone system may have been affected earlier than the rods. If this is the case then psychophysical procedures such as dark adaptation would be of great importance to use in studying MS.

Throughout this discussion, the loss in cone functioning has not been assumed to be structural -- at least not in the early stages of the disease. The reason for this comes from the attempted pilot study on modifying adaptation threshold. By having MS subjects close their tested eye for a period of 2 minutes, thereby altering the state of retinal adaptation, foveal thresholds were dramatically lowered. As this change in threshold did not appear to be due to a change in fatigue, it is assumed that the initial higher threshold was not due to the presence of structural damage, i.e., at least not permanent structural change. If the damage was permanent, one would not have expected improvement in the threshold. Similar results regarding the effects of variable background luminances on MS has been reported by Patterson, Foster and Heron (1980).

Patterson et. al. reported that threshold variability

\[\text{Although the mean threshold difference at the fovea between the normals and MS-probables was not significant, it is felt that if the fovea was analyzed separately a significant difference would have been found.}\]
increased with increasing background luminance in MS but not normal control subjects, suggesting some type of fluctuating interference with the visual signal. This is in agreement with the present study in that the standard deviations for the 2 MS groups under the 45 asb. background condition is much greater than that of the normals.

Fluctuations in cone functioning, as evidenced in the pilot study, may explain temporary losses seen in MS patients with respect to complaints about visual acuity. More importantly, by altering the adaptational state, one may be able to establish which of the receptor systems was affected the earliest in the disease process. Thus, by examining receptor functioning under fully photopic and fully scotopic levels, one should be able to isolate which of the systems is involved. As the present study used a background luminance level (45 asb.) at the lower end of the photopic range, one would have expected better cone functioning if the cone system was not affected. As the reverse was true, the results argue that it is the cone system which is affected the most. As the course of the disease progresses, and the damage becomes more extensive, the cone system becomes indistinguishable from the rod in the former's sensitivity to chromatic stimuli.

The question that arises is what may be responsible for the observed threshold differences. Because of the
relationship of optic neuritis (ON) to MS, it is possible that ON may provide a partial explanation.

The optic nerve is estimated to contain roughly 1.1 to 1.3 million nerve fibres as well as other supportive elements (Newell, 1978). It may be divided into 4 anatomical sections:
1. intraocular,
2. orbital,
3. intracanalicular, and
4. intracranial.

The intraocular section is unmyelinated (except in pathological cases) and consists of the inner retina, the middle choroidal, and the outer scleral. The inner retina is viewed ophthalmoscopically as the optic disk.

Concentric to the optic disk is a central depression known as the physiologic cup. It is through the cup that the central artery and vein enter and leave the eye. Inside the cup are small pore like structures (lamina cribosa) that connect with the scleral foramen. It is at this juncture where the optic nerve itself passes in and out of the eye.

The optic nerve itself is comprised of afferent axons of ganglion cells collectively called nerve fibre bundles. The bundles are separated by septa that carry blood vessels to the nerve. The axons of the retinal ganglion cells are spread in a radial fashion around the innermost surface of the retinal layer, converging at
the optic disc. Normally, this retinal nerve fibre layer (RNFL) is slightly opaque and appear as fine striped striations in the temporal and nasal retina (Airaksinen & Nieminen, 1985). In diseases such as glaucoma, however, diffuse and localized losses in various regions can be detected prior to any measureable changes in the optic disc itself (Airaksinen & Alanko, 1983). The losses themselves are found as thining of the RNFL due to damage of the axon layer. Recently, RNFL loss has been shown to be highly correlated with colour discrimination losses on the anomalscope in glaucomatous patients (Airaksinen, Lakowski & Drance, 1986).

In optic neuropathies, Tagami (1979) reported central field depression on the Tübinger perimeter correlated highly with the degree of observed atrophy in maculopapillar bundles. Although Tagami tested retrobulbar neuritis patients with an achromatic stimulus, the central loss observed is interesting as it, along with the findings on glaucoma, suggests that the maculopapillar region is responsible for conveying visual information such as colour vision and acuity back to the optic disc. Moreover, it is this region which appears to be the most sensitive to pathological processes.

In the case of MS, examination of the retinal layer has revealed the presence of diffuse and focal damage, especially of the temporal peripapillary bundles
(Feinsold & Hoyt, 1975). In addition, there tends to be slit-like defects in the arcuate nerve fibres. As this defect pattern is similar to the ones reported by Tagami (1979) and Airaksinen et al. (1986), it would seem likely that the threshold losses observed in the present study were partially due to RNFL loss in the maculopapillar region. The loss within this region would correspond to the large central depressions observed among the MS patients for the various filters.

If this is the case, a question then arises about the losses reported in MS as related to that disease's progression. Tagami (1979) argued that RNFL loss tended to occur outside the fovea in the temporal region of the retina. The finding from the present study of increased thresholds in the nasal visual field (temporal side of the retina) would appear to indicate a similar loss in MS. If this is the case, the distribution of the various cones may provide some answer to this finding. It has long been accepted, based upon kinetic perimetry, that the relative frequency distributions of the various cones differs at the retina. It is typically felt that the fovea itself (1/8°) is blue blind (Adler, 1975) and that the red sensitive cones are maximally situated there. The blue and green wavelength sensitive cones are distributed away from this region. Trichromatic vision itself extends about 20° to 30° from fixation (Adler, 1975). As RNFL loss appears to spare the fovea in the
early stages of disease, red cone functioning remains relatively intact until the retinal system is stressed as in conditions of increased background illumination. Once in such stressful visual situations, abnormalities in red cone functioning appear. As it would appear that the red cone system may play a part in the resolution of high spatial frequencies, one would theoretically expect disturbances in visual acuity under such stressful conditions. It is interesting to note that a common clinical symptom reported about MS is early, temporary fluctuations in acuity. These fluctuations may result from abnormal processing at the cone level in the fovea, and, if Lennie (1980) is correct in his statement that \( w \) retinal ganglion cells are maximally found at and around the fovea, it is possible that the \( w \) cells (carrying information mostly from the red cone system) are least susceptible to structural damage. It must be stressed that this does not mean there is no psychophysical loss for evidently losses do occur (eg. presence of red-green losses as noted by Lakowski, Harrison and Stell (1985). Because an area appears to be anatomically intact, it does not follow that it is functionally intact. Given the correct visual conditions (eg. higher background adaptation) and the appropriate psychophysical procedure (eg. chromatic flicker perimetry), changes in specific types of visual functioning may become apparent.
If the line of reasoning here is valid, one might be able to hypothesize on the progression of MS with respect to retinal functioning. The present study found that there were slightly more significant correlations with the blue filter than the red, keeping in mind however that such a trend depends highly upon the adaptational state. Such a pattern could be interpreted as meaning that the blue system was affected the most. As the blue cones tend to be typically just outside 0° eccentricity, the thinning of the RNFL in the temporal part of the maculopapillar region may represent disturbance in blue cone conduction. It is conceivable that early blue cone function loss may predict RNFL loss in this region. The red cone system, though also affected by MS, tends not to show functional change early unless the system is placed in a visually stressful situation (eg. high background luminance conditions found in glare). As the disease progresses, the red cone system becomes more impaired until permanent dysfunctions such as loss in visual acuity is seen. The damage continues until the cone system is no longer functionally distinct than the rods, both requiring large increases in intensity. As noted in the literature, disturbances in luminance perception is also observed in the progression of MS, suggesting possible higher cortical involvement than has been suggested.

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1Yellow-blue losses have been reported by Lakowski, Harrison and Stell (1985).
here. Further research involving flicker perimetry will be needed to investigate the possible role of higher cortical centres.

b. Methodological and Instrumental Problems

Several problems affect the results and interpretations presented here. First and foremost is the psychophysics of the Fieldmaster® bowl. Unlike the majority of perimeters whereby a stimulus is projected onto a bowl that has some constant level of illumination, the background luminance level in the F225 does not appear to play a significant role. The reason for this is that the fiber optic system does not project a stimulus onto the bowl but directly to the eye. Thus, unlike other perimeters, the foveal threshold obtained with the F225 was much lower than normally seen. Moreover as the center of the fibre optic, when not being illuminated, was darker than the bowl, subjects were not only detecting changes in stimulus luminance but luminance contrast differences between the fibre optic position and adjacent surround. As photometrically the bowl was shown not to be equivalent in luminance, especially at the point of fixation, the changes in the center of the visual threshold for the MS patients may have been due to an abnormal lateral inhibition caused by the luminance contrast. Aulhorn and Harms (1972) have reported reduced thresholds due to the presence of such
luminance border contrasts. This however would appear unlikely in the present study as the point used to conduct the foveal examination, as well as the other eccentricities occurred away from the regions of differing lumination. If the luminance difference between the fibre optic and surround played a significant role, its effects should have been constant across the retina (only if, of course, inhibition is the same across the retina).

Because of the fibre optic system used, the background bowl level may function only to "ready" the retina at some general level of adaptation (here the lower photopic range). It does not play a role in determining threshold levels, and, as such, normal psychophysical laws as the Weber fraction which is based on background level probably do not apply. Thus it makes it extremely difficult to compare the present results with those reported with other perimeters such as the Goldmann.

Another problem with the results is the manner in which thresholds are determined by the F225. If a blink occurs during testing, the computer algorithm increases the intensity level for that eccentricity. Instead of retesting that eccentricity with the same luminance level, the programme stores the blink as not seen at that threshold. Although not a problem earlier in the test sequence, this does become extremely important near
the end of testing for it will provide the operator with a falsely raised threshold. The only way of overcoming this problem is to redesign the computer programme to re-test a point where fixation has changed (eye movement, blink etc.) with the same luminance level.

Problems also arose with respect to the treatment of thresholds exceeding 1,000 asb. Because of time constraints with the patients, the maximum intensity stimuli were presented at was 1,000 asb. If not seen at that level, the patient or normal was assigned that maximum value. This in effect may have biased the results by reducing the range of the actual threshold difference.

In addition to altering how the perimeter re-tests a missed point due to a problem in fixation, changes need to be made in the incremental steps used to change stimulus intensity. For the fovea the steps should be about .1 cd/m², which is much smaller than the 1 decibel step presently used.

Fixation is another major problem. Although the reliabilities were high with the F225, the allowed 5° eye movement is too great for research purposes. More control is required in monitoring the eye prior to any further research. In the case of the F225 this will require adapting some external monitor to the perimeter.
In controlling the perimeter, it is recommended to bypass the LSI computer by interfacing the F225 with another, more flexible computer. This will permit the research to collect invaluable data such as the actual apostilb level presented, one which is only presented in graph form. The thermal graph used is both time consuming when trying to interpolate values as well as problematic for storage: the thermal graph fades with time or exposure to any heat.

Other methodological problems may have affected the interpretation of the results. First, there is no severity index for the MS patients. It would have been important to have some external severity score as to the disability of the MS if conclusions about the progressive effects of the severity of the disease are to be made. Moreover, it would have been desirable to have included a group of patients who were just suspected of having MS and compare these to patients who have been clinically verified as having it for a long period of time. In fact, what is needed is a longitudinal psychophysical study on MS.

Another problem was the inability to alter rigorously the adaptational state. Without doing so, it is impossible to draw any systematic conclusions about the role of rods and cones in MS. Unfortunately the F225 did not allow for a controlled investigation into the effects of adaptation.
c. Future Research

The results of the study suggest several research avenues in studying the effects of MS. First, a more intensive investigation is needed regarding psychophysical functioning of the retina. In order to isolate the relative contributions of the two receptor systems, it will be necessary to alter background intensities from the fully photopic to the fully scotopic. This will also require the use of photometrically equated chromatic and achromatic stimuli.

Secondly, to understand temporal properties, the investigation should examine specific cone functioning (for the red, blue, and green systems) through the chromatic flicker threshold technique using low flicker rates. The procedure may be done under selective chromatic adaptation so as to understand cone functioning in greater detail than has ever been possible before. By doing so, information regarding temporal processing in the retina will be obtained.

Similarly, temporal processing in the cone system can be studied by measuring achromatic functional changes through the chromatic flicker threshold technique at high flicker rates (eg. 24 Hz). Data obtained from such a procedure will provide information on the luminance channel. All of the research suggested
here, of course, will need to be done on normal populations in order to determine overall normal psychophysical functioning prior to studying MS and its effects.

In conjunction with the psychophysical approach, data regarding structural changes in the retina (eg. RNFL) needs to be collected. It would be extremely valuable clinically to correlate psychophysical changes with the anatomical, especially since the psychophysical change probably occurs prior to any structural change. Moreover, the noninvasive nature of psychophysical assessment makes it a more desirable procedure to use clinically. Using cut-off log apostilb threshold values such as -2.45 for the blue, -2.25 for the red, and -2.50 for the achromatic one may be able to examine clinical (visual) changes in the progression of MS more precisely than was previously possible. That is, these values may be used to develop visual threshold profiles, which in turn could be used not only for assisting in the diagnosis of MS but also serving as the basis of a 'visual' severity index.

As the cone system appears to be the most sensitive to the presence of a pathological state, here MS, further clinical and experimental research needs to focus upon macular functioning. Visual evoked potential procedures, for example, may be improved by using chromatic stimuli at photopic adaptation levels inorder
to improve the detection rate of an abnormality. In all, what is need, is an extensive prospective study whereby at risk patients are followed through their clinical history with an intensive examination of rod/cone functioning. It is strongly felt that the information gained through such an approach would not only tell us something about the nature of MS but also provide invaluable insight into visual functioning.
VI. SUMMARY

Through the use of chromatic static perimetry, it was established that threshold losses occur across the retina in MS patients. The losses appear to be greater for the cone system rather than the rod, as inferred from the greater losses with the chromatic rather than achromatic filters. Significant differences were found at the $0^\circ$ eccentricity between the normal and clinically definite patients but not the probable and normal. This may have indicated the sparing of the $0^\circ$ eccentricity in nonestablished cases of MS. Such an interpretation needs to be guarded due to problems in monitoring eye movement as well as the lack of a severity index.

Differences were found in the filters, with the blue showing slightly more significant mean differences than the red or achromatic between the 3 subject groups. Both the comparison of mean differences as well as correlations between the fovea and remaining eccentricities revealed extensive involvement of the retina among the MS patients as compared to the normals. Threshold differences between the filters due to eccentricity was also noted across groups, and was felt to reflect the selective sensitivity of the rod/cone system to chromatic stimuli. An investigation of patients with and without optic neuritis revealed no overall significant differences except for the differential sensitivity across the retina to chromatic and achromatic
stimuli.

The typical swiss cheese field resulting from irregular threshold sensitivity across the eccentricities reported in the clinical literature appears to be true only for achromatic and blue stimuli. No such irregularity appears for a red stimulus. As such, the ophthalmological description of MS consisting of patchy relative scotoma leading to the swiss cheese field defect needs to be qualified.

The importance of assessing MS through chromatic static perimetry was also demonstrated by the ability to correctly classify 86.27% of the normals and MS patients by the red filter. This high level of diagnostic accuracy along with the ability to examine specific cone/rod functioning indicates the invaluable information available through chromatic perimetry.

Results from a pilot study indicated that adaptation state plays a major role in detecting relative threshold losses in MS. Unfortunately, the present state of the F225 did not permit further investigation into the effects of adaptational state.

In all, retinal functioning as assessed with the Fieldmaster® F225 has been shown to be highly sensitive to changes due to the presence of MS (with or without optic neuritis). The findings suggest that a more intensive examination of cone functioning may yield significant understanding of the disease process as well as the means to
both detect and chart the progression of the disease.
BIBLIOGRAPHY


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VII. APPENDIX A
1. **POWER SUPPLY**

The **F225** has four separate power supply units. These are: (1) the thermal printer power supply, (2) the computer power supply, (3) the analog power supply, and (4) the **Fieldmaster®** power supply.

a. **Thermal Printer Power Supply**

The power source to the thermal printer is a switching power supply rated at 15 volts and 15 amps, which is suitable for the Synemed TP640 Thermal Printer. The supply (Lambda Model No. LYS-W-15) is preset to provide the proper voltage for the individual printheads on the printer. There are two printheads, each colour coded so as to identify them both on the thermal printer and power supply unit. The two printheads are:

- a. Blue coded -- 16.0 volts
- b. Brown coded -- 17.0 volts

b. **Computer Power Supply**

The power supply (Lambda Model No. LYS-W-15) to the computer operates the basic functioning of the **F225** including background and stimulus intensity control,
visual field screening, and relative threshold estimation. The power supply has three different outputs that are factory preset, which are:

- a. +5.05 volts
- b. +12.0 volts
- c. -12.0 volts.

c. Analog Power Supply

The analog power supply (Model No. HAA-15-0.8) provides power to the analog section of the F225. The analog board, discussed elsewhere, is a signal processing board that buffers and amplifies analog signals. It is factory preset to produce two voltages at:

- a. +15.0 volts
- b. -15.0 volts.

d. Fieldmaster® Power Supply

The Fieldmaster® power supply is constructed to provide voltage to the background luminance, stimulus luminance, and stepper motor. It is housed in a moveable section under the table of the F225. The bowl of the
F22f perimeter is connected to the power supply via a 37 pin connector, which must be disconnected when removing or connecting the F225 bowl from the table.

The F225 power supply is shielded from transient fluctuations in the A.C. power line by a L-C filter circuit. Examination of the power supply itself can be done by looking at the indicator LED's found in the instrument shell on the Monitor card (to be discussed). When functioning normally, the LED's will be all lit. The power supply outputs are:

- a. 0 to +13.0 volts for the background bulb
- b. +5.8 volts for the stimulus bulb
- c. +12.0 volts for the stepper motor.

2. INSTRUMENT SHELL

The F225 is operated by an LSI-11/2 Digital Equipment Corporation (DEC) computer. The LSI-11/2 is found in a card cage fixed to the lower right hand side of the instrument shell when viewed from the back of the perimeter (see Figure x). The card cage itself consists of a backplane (DEC No. H9275A) that has four dual and two quad height p.c. boards. The backplane is basically a skeletal structure that connects the various c.p. boards to one another and to sections of the perimeter. Power is supplied through a source located in
the back of the card cage on top of the backplane itself. For a discussion of the terms used in this section the reader is referred to *Laboratory computer handbook* and *Microcomputers and memories* published by the Digital Equipment Corporation.

The following are the various boards found in the **F225** perimeter.

a. 1. Central Processing Unit

The central processing unit, or CPU board is a dual height p.c. board found in the lower left hand corner of the card cage marked "1B". It is used with the optimal floating point instruction (DEC No. KEV11) set and contains the actual computer processor (stored programmes). The different functions possible with the CPU is described under the section referred to as Visual Test Functions.

The CPU is jumper-configured to *jump* to address address "0" when the power is turned on. Above the CPU card, in slot "1A", is another p.c. board known as the Grant Extender. The Grant Extender (Synemed No. 160-11519) passes backplane signals to other boards and permits the cooling of various p.c. boards in the card cage.
b. Serial/Memory Board

The serial/memory board is found in slot "2B" of the card cage. It is a dual height p.c. board (DEC No. MXV11-AA) and consists of 8k bytes of random access memory (RAM) and two serial ports. RAM is addressed from the octal memory locations 140000 to 157776. The first serial port, port 1, is a standard RS232 interface with a baud rate of 300. Addressed at the memory location 177560, it is connected through a DB25 (25 pin) connector found on the instrument case. The F225 does not use serial port 0 for any operation.

c. Image Board

The other dual height p.c. board is the image board, located in slot "8A". The board consists of read-only-memory (ROM). The ROM card (DEC No. MRV11-C) contains fixed information such as box lines, degree lines, and header labels used in generating printer output. Output information may be either obtained automatically at the end of each run or by request of the operator. Information in this board is processed through a 4k byte "window" found in memory locations 160000 to 16776.
d. Printer Control Board

The printer control board, found in slot "4A", is a quad height p.c. board. Its function is to transfer data to the thermal printheads through the printer drive board. In addition, the printer control board interfaces the print cycle timing (on and off time for generating plots) and print control (information from the image board). Next to this are two Grant Extenders (slots "5A" and "5B"), which are used to pass bus signals as well as cool the various boards in the card cage.

e. Interface Board

Another quad p.c. board, the interface board, is found to the right of the Grant Extenders (slots "6A" and "6B"). This board connects the DEC LSI-11/2 computer with various F225 functions (eg. stimulus control) and consists of the following parts.

f. Digital-Analog Convertor

The digital to analog convertor (DAC) consists of various circuits including a DAC1220 twelve bit convertor (Z2). The DAC enables the LSI-11/2 to control the background level in the perimetry bowl through the background drive going to the Fieldmaster® Power Supply. This is accomplished by the LSI-11/2 sending twelve bit
signals to the DAC, thereby producing an analog drive signal for the Fieldmaster® Power Supply. The DAC itself is powered by a voltage regulator (Z10) that allows the analog output to range from 0 to +10.24 volts.

g. Analog-Digital Convertor

The analog to digital convertor (ADC) is comprised of an ADC1210 twelve bit convertor (Z5), which enables the computer to record and monitor analog information from eight channels. The analog signals from the eight channels are directed into an analog multiplexer (Z7) to the DAC.

- Channel 1 Stimulus level
- Channel 2 Stimulus level X 22.1¹
- Channel 3 Background level
- Channel 4 Attention monitor (x plane)
- Channel 5 Attention monitor (y plane)
- Channel 6 Attention monitor common mode
- Channel 7 Analog ground
- Channel 8 Analog ground

¹ The multiplication value of 22.1 in the second channel is to increase resolution at lower light levels so as to be able to accurately record stimulus intensity. Both channels 1 and 2 overlap, making it possible to provide measures of levels continuously from high (30,000 asb) to low (x asb) stimulus intensities.
h. Permanent Memory

Permanent memory consists of a RAM chip (1k by 4 byt). In addition, there are two batteries serving as power back-up in case of power failure from the Fieldmaster® Power Supply. The permanent memory chip stores test information obtained from a test run.

i. Attention Monitor Targets

Both the attention monitor and macula target (discussed elsewhere) are monitored for intensities. The monitors are powered by signals from the background preamplifier (BGLVL) and are adjusted by the chips R70 (macula target) and R71 (attention monitor).

j. Alarm

Alarms are produced when either the attention monitor detects gross changes in the subject's position or when testing is completed. An alarm is also activated during testing when there is some problem with the perimeter itself (discussed in the section on error feedback -- Appendix x). The alarm itself is produced by a timer and can be amplified by the Z14 chip and adjusted by the R71.
k. Stepper Drive

There are three stepper motors, the drive for which is on the interface board. The first stepper motor operates the selector arm (selects stimulus position) and the drive output for it is found on pins 9, 10, 11, and 12 on the P8 connector. The second stepper motor controls the stimulus intensity wedge, which is done through pins 7, 8, 13, and 14. The final stepper motor operates the stimulus colour filter through pins 3, 4, 5, and 6.

1. Programme Board

The programme board is below the serial/memory card in slot "2A". It is read-only-memory (ROM) and stores the operating programmes available on the F225. The board (DEC No. MRV11-C) has 48 bytes comprised of 12 Intel 2732 EPROM's. The EPROM's contain the actual programmes from Synemed. When started, the programme board automatically is configured to start at address 0. To the right of the board are two Grant Extenders used for cooling.

m. Monitor Board

The monitor board is found on the left of the card cage, and is recognizable by ten LED's (eight green, one
red, and one yellow). The red LED, when on, indicates the presence of a fault at which time the instrument powers down stopping all testing. See Appendix D for a list of possible errors. The yellow LED indicates normal functioning, and turns off when either a fault is detected or the RUN/HALT switch (discussed shortly) is toggled.

The eight green LEDs indicate the functioning of threshold comparators that monitor power voltages in the various areas of the perimeter. A green LED will be turned off when its associated voltage comparator senses a drop in the voltage of a specific power supply. At the same time a drop in voltage is sensed, the red fault LED will be turned on and the cpu card begins to power down the perimeter immediately. The following is a list of what threshold voltages are associated with a specific green LED.

- a. LED #1 voltage = -15 V., threshold voltage = -12.2 V.
- b. LED #2 voltage = +12 V. (Fieldmaster® Power Supply), threshold voltage = +11.0 V.
- c. LED #3 voltage = +17 V. (Thermal Printer Power Supply), threshold voltage = +14.0 V.
- d. LED #4 voltage = +15 V., threshold voltage = +12.2 V.
- e. LED #5 voltage = +5.8 V. (Stimulus Supply),
threshold voltage = +4.99 V.
- f. LED #6 voltage = -12.0 V., voltage = -11.0 V.
- g. LED #7 voltage = +5.0 V. (Computer Power Supply), voltage = +4.42 V.
- h. LED #8 voltage = +12.0 V. (Computer Power Supply), voltage = +11.0 V.

In addition to the sensing of a change in the power voltage for sections like the power supply to the computer (8,9) or printer (3), wherein if the threshold voltages listed above are reached a power down sequence commences, two buss signals (BPOK and BDCOK) monitor voltage changes from the A.C. line.

The monitor board also contains two toggle switches used to either power down or power up the perimeter during troubleshooting. Both switches during normal operation are in the down position. The first switch on the left hand side, the RUN/HALT switch, is used to power down the perimeter. This is done by toggling the RUN/HALT switch into the up position, causing the yellow LED to go off and, at the same time, the red to go on. The second switch on the right hand side of the monitor board is the INIT switch (initialize switch). The INIT switch is used to initialize the LSI-11/2 into running mode. To initialize, the RUN/HALT switch must be in the down position and the INIT switch toggled first up and then down. If done correctly, the yellow (running light)
LED will be on. When connecting any minicomputer or other peripheral to the perimeter for the purpose of debugging problems or increasing the capabilities (eg. storage) of the 225, it is extremely useful to remove the back plate of the perimeter so as to have access to the switches and observe the LEDs on the monitor board.

n. Analog Board

The analog board is found on the left near to the monitor board. Its function is to buffer and amplify signals coming from the attention monitor, the background preamplifier, and the stimulus preamplifier. Input to the analog board arrive on a 26 pin Berg connector (P6) and exit through a 10 pin flat cable to the multiplexer. All signals from the analog board go directly to the interface board through the multiplexer.

o. Attention Monitor Board

The monitor consists of a photodetector that doubles as an amplifier. Reflection off the cornea is imaged onto four quadrants of a photodetector housed in an optical telescope assembly. Quadrants 1 and 3 of the photodetector create currents whose values represent changes in the reflected light from the cornea. These changes, representing eye movements, are then summed and passed onto the analog board. Similarly, quadrants 2
and 4 pass their produced current changes whose sum is sent to the analog board. The values from the various quadrants are converted to voltages prior to transmission.

p. Background Preamplifier

A photodiode constantly measures the background illumination in the bowl. The photodiode creates a current that is directly proportional to the luminance level in the hemisphere. Through a voltage convertor (Z1), the current is then changed into a voltage value that is processed to the analog board. Signals from the preamplifier are enhanced by a "background amplifier" that increases the current value by a factor of 2.2. This is done so as to increase the "sensitivity" of the photodiode, i.e. small fluctuations in the current are registered.

q. Stimulus Preamplifier

Stimulus intensity is monitored by sampling the filtered light from the main projection beam. The actual intensity, monitored by a photodiode, is amplified through two voltage convertors (Z1, Z2) and is corrected for non-linearity. Two other photodiodes are used to adjust the stimulus intensity calibration. The calibration adjustment occurs in conjunction with the
non-linear correction of luminous intensity. The manual on the F225 refers to the adjustment of stimulus intensity as *slope correction preamplification*. Output from the stimulus preamplifiers goes directly to the Analog board wherein the various signals (attention monitor, background and stimulus intensity levels) are processed toward the the Interface board.

r. Projector/Shutter/Filter Assembly

This unit, situated on top of the Selector Board, converges the projected beam of light onto a selector arm light conduit. Through stepper motors controlled by the LSI-11, two (2) filter wheels rotate around an aperture from which the projected beam is passed through the filter wheels onto the fibre optics. One filter wheel consists of neutral density filters used for controlling stimulus intensity whereas the other filter wheel is comprised of 4 Kodak Wratten Filters (λ 632.7, 581.2, 533.8, 489.3 nm.) and one achromatic filter. The latter filter, refered to as the *wedge colour*, is operated through a separate stepper motor than the neutral density filter. Both filter wheels are controlled by the Interface Board.

In addition, the assembly contains photodiodes responsible for stimulus preamplifications as well as a shutter for controlling stimulus presentation.
s. Selector Board

The board is located centrally on the bottom of the instrument housing. It contains 149 fibre optic strands that form a circular pattern radially from a motor driven arm. A light conduit on the arm projects a light beam, originally directed to the center of the arm's rotation, to specific optic fibres as determined by the operator defined programme. The actual position of the motor driven arm is controlled by a stepper motor operated by the Interface board.
VIII. APPENDIX B

Photometric Bowl Measurements
### Photometric Measurements

**In Apostilbs (ABS.) and Candella/Meter (CD/M-2)
Of Background Intensities by Stimulus Position**

In the Fieldmaster F225 Perimeter*

<table>
<thead>
<tr>
<th>Background Intensity (Apostilbs)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABS.</strong></td>
<td>0.81</td>
<td>0.83</td>
<td>0.88</td>
<td>0.87</td>
<td>0.75</td>
<td>0.95</td>
<td>0.89</td>
<td>0.80</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>0.26</td>
<td>0.26</td>
<td>0.28</td>
<td>0.28</td>
<td>0.24</td>
<td>0.24</td>
<td>0.22</td>
<td>0.22</td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>ABS.</strong></td>
<td>4.75</td>
<td>4.59</td>
<td>4.39</td>
<td>4.56</td>
<td>3.19</td>
<td>0.69</td>
<td>2.56</td>
<td>4.27</td>
<td>4.51</td>
<td>4.53</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>1.51</td>
<td>1.46</td>
<td>1.40</td>
<td>1.45</td>
<td>1.01</td>
<td>0.22</td>
<td>0.81</td>
<td>1.36</td>
<td>1.44</td>
<td>1.44</td>
</tr>
<tr>
<td><strong>ABS.</strong></td>
<td>10.58</td>
<td>10.43</td>
<td>10.16</td>
<td>10.39</td>
<td>7.29</td>
<td>1.79</td>
<td>5.75</td>
<td>9.64</td>
<td>10.29</td>
<td>10.25</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>3.33</td>
<td>3.32</td>
<td>3.23</td>
<td>3.31</td>
<td>2.32</td>
<td>2.57</td>
<td>1.83</td>
<td>3.07</td>
<td>3.28</td>
<td>3.26</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>5.08</td>
<td>5.25</td>
<td>5.22</td>
<td>5.22</td>
<td>3.63</td>
<td>0.95</td>
<td>2.90</td>
<td>4.89</td>
<td>5.22</td>
<td>5.16</td>
</tr>
<tr>
<td><strong>ABS.</strong></td>
<td>35.28</td>
<td>34.61</td>
<td>34.15</td>
<td>34.12</td>
<td>24.12</td>
<td>6.16</td>
<td>19.08</td>
<td>32.27</td>
<td>34.42</td>
<td>33.83</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>11.14</td>
<td>11.02</td>
<td>10.87</td>
<td>10.86</td>
<td>7.68</td>
<td>1.96</td>
<td>6.08</td>
<td>10.37</td>
<td>10.96</td>
<td>10.77</td>
</tr>
<tr>
<td><strong>ABS.</strong></td>
<td>53.78</td>
<td>53.38</td>
<td>52.69</td>
<td>52.76</td>
<td>36.68</td>
<td>8.73</td>
<td>29.08</td>
<td>49.53</td>
<td>52.76</td>
<td>52.25</td>
</tr>
<tr>
<td><strong>ABS.</strong></td>
<td>59.75</td>
<td>58.95</td>
<td>58.09</td>
<td>58.49</td>
<td>40.74</td>
<td>9.49</td>
<td>32.26</td>
<td>54.95</td>
<td>58.29</td>
<td>57.42</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>18.83</td>
<td>18.76</td>
<td>18.49</td>
<td>18.62</td>
<td>12.97</td>
<td>3.02</td>
<td>10.27</td>
<td>17.49</td>
<td>18.56</td>
<td>18.28</td>
</tr>
<tr>
<td><strong>ABS.</strong></td>
<td>61.04</td>
<td>59.79</td>
<td>58.89</td>
<td>58.65</td>
<td>40.68</td>
<td>9.49</td>
<td>32.22</td>
<td>54.85</td>
<td>58.28</td>
<td>57.42</td>
</tr>
<tr>
<td><strong>CD/M-2</strong></td>
<td>19.18</td>
<td>19.03</td>
<td>18.75</td>
<td>18.67</td>
<td>12.95</td>
<td>3.02</td>
<td>10.26</td>
<td>17.46</td>
<td>18.55</td>
<td>18.23</td>
</tr>
</tbody>
</table>

*Note: Values presented are based on the mean of 3 measurements done on each stimulus position.*
PHOTOMETRIC MEASUREMENTS
IN APOSTILBS (ABS.) AND CANDELLA/METER (CD/M-2)
OF BACKGROUND INTENSITIES BY STIMULUS POSITION
IN THE FIELDMASTER F225 PERIMETER*

<table>
<thead>
<tr>
<th>BACKGROUND INTENSITY (APOSTILBS)</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ABS.</td>
<td>0.81</td>
<td>0.85</td>
<td>0.78</td>
<td>0.85</td>
<td>0.89</td>
<td>0.78</td>
<td>0.84</td>
<td>0.93</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>CD/M-2</td>
<td>0.26</td>
<td>0.27</td>
<td>0.25</td>
<td>0.27</td>
<td>0.27</td>
<td>0.28</td>
<td>0.25</td>
<td>0.27</td>
<td>0.30</td>
<td>0.26</td>
</tr>
<tr>
<td>CD/M-2</td>
<td>1.41</td>
<td>1.40</td>
<td>1.38</td>
<td>1.44</td>
<td>1.45</td>
<td>1.39</td>
<td>1.30</td>
<td>1.42</td>
<td>1.39</td>
<td>1.35</td>
</tr>
<tr>
<td>CD/M-2</td>
<td>3.17</td>
<td>3.16</td>
<td>3.21</td>
<td>3.25</td>
<td>3.22</td>
<td>3.18</td>
<td>2.96</td>
<td>3.28</td>
<td>3.26</td>
<td>3.13</td>
</tr>
<tr>
<td>15 ABS.</td>
<td>15.95</td>
<td>15.74</td>
<td>15.89</td>
<td>16.24</td>
<td>16.21</td>
<td>15.93</td>
<td>14.89</td>
<td>16.35</td>
<td>16.13</td>
<td>15.53</td>
</tr>
<tr>
<td>CD/M-2</td>
<td>5.08</td>
<td>5.01</td>
<td>5.06</td>
<td>5.17</td>
<td>5.16</td>
<td>5.07</td>
<td>4.74</td>
<td>5.20</td>
<td>5.13</td>
<td>4.94</td>
</tr>
<tr>
<td>30 ABS.</td>
<td>33.69</td>
<td>33.05</td>
<td>33.52</td>
<td>34.09</td>
<td>34.21</td>
<td>33.30</td>
<td>31.30</td>
<td>34.25</td>
<td>34.11</td>
<td>32.15</td>
</tr>
<tr>
<td>CD/M-2</td>
<td>10.72</td>
<td>10.52</td>
<td>10.67</td>
<td>10.85</td>
<td>10.89</td>
<td>10.60</td>
<td>9.96</td>
<td>10.90</td>
<td>10.86</td>
<td>10.23</td>
</tr>
<tr>
<td>45 ABS.</td>
<td>50.99</td>
<td>50.71</td>
<td>51.11</td>
<td>52.06</td>
<td>52.64</td>
<td>51.59</td>
<td>47.65</td>
<td>52.84</td>
<td>52.59</td>
<td>49.57</td>
</tr>
<tr>
<td>50 ABS.</td>
<td>55.91</td>
<td>55.10</td>
<td>55.51</td>
<td>56.77</td>
<td>56.85</td>
<td>55.66</td>
<td>51.74</td>
<td>56.73</td>
<td>56.63</td>
<td>53.19</td>
</tr>
<tr>
<td>CD/M-2</td>
<td>17.80</td>
<td>17.54</td>
<td>17.67</td>
<td>18.07</td>
<td>18.10</td>
<td>17.72</td>
<td>16.47</td>
<td>18.06</td>
<td>18.03</td>
<td>16.93</td>
</tr>
<tr>
<td>55 ABS.</td>
<td>55.82</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD/M-2</td>
<td>17.77</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: * - Values presented are based on the mean of 3 measurements done on each stimulus position.
IX. APPENDIX C

F225 Automatic Visual Field Programmes
1. CONTENTS

The visual field programmes are copyright and are available from Synemed upon written request.
X. APPENDIX D

F225 Automatic Contour Programmes
1. CONTENTS

The contour programmes are copywrited and are available from Synemed upon written request.
XI. APPENDIX E

F225 Automatic Meridian Programmes
The meridian programmes are copywrited and are available from Synemed upon written request.
XII. APPENDIX F
1. COMPUTER INTERFACE

The Fieldmaster® F225 uses a Digital LSI 11/2 microcomputer both for programme execution and communicating with another host. The LSI can be used in a special debugging mode known as Octal Debugging Technique (ODT). The system to be connected through a serial link with the F225 must appear as a terminal to the LSI 11/2. The serial link is through a RS-232c already found in the Fieldmaster.

The communications port on the host computer will connect to its counterpart on the Fieldmaster through pins 2, 3, and 7 on the RS-232. Signals from any of the other pins will be ignored. The host computer must be set on the following specifications:
1. 8 bits, no parity
2. 1 stop bit
3. 300 Baud rate

Once connected, threshold information may be obtained in octal values from two memory locations starting at 144650 for intensity seen and 144742 for intensity not seen. By transforming the octal values into the decimal system and averaging the seen/not seen intensity values, one obtains the threshold for each eccentricity tested.
XIII. APPENDIX G
### Multivariate Analysis of Variance between Normals (n=30), Optic Neuritis (n=8), and Non Optic Neuritis (n=14) MS Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (G)</td>
<td>48511962.29</td>
<td>2.49</td>
<td>24255981.14</td>
<td>18.06</td>
<td>.0000</td>
</tr>
<tr>
<td>Filter (F)</td>
<td>13381983.78</td>
<td>2.98</td>
<td>6690991.89</td>
<td>104.52</td>
<td>.0000*</td>
</tr>
<tr>
<td>Eccentricity (E)</td>
<td>33959267.43</td>
<td>3.70,181.54</td>
<td>2612251.34</td>
<td>42.85</td>
<td>.0000*</td>
</tr>
<tr>
<td>G X F</td>
<td>464663.53</td>
<td>2.86,70.01</td>
<td>116165.88</td>
<td>1.81</td>
<td>.1550*</td>
</tr>
<tr>
<td>G X E</td>
<td>4099006.93</td>
<td>7.41,181.54</td>
<td>157654.11</td>
<td>2.59</td>
<td>.0128*</td>
</tr>
<tr>
<td>F X E</td>
<td>4878008.39</td>
<td>11.57,567.06</td>
<td>187615.71</td>
<td>14.11</td>
<td>.0000*</td>
</tr>
<tr>
<td>G X F X E</td>
<td>1929719.11</td>
<td>23.14,567.06</td>
<td>37109.98</td>
<td>2.79</td>
<td>.0000*</td>
</tr>
</tbody>
</table>

**Note:** * Denotes probability after degrees of freedom have been adjusted by the Greenhouse-Geisser.