TO MY PARENTS

THE EFFECT ON VISUAL ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL INVESTIGATIONS OF SUBSTANCES PRIMARILY INDUCING A DELETERIOUS EFFECT ON THE RETINAL GANGLION CELLS AND/ OR HIGHER UP THE VISUAL PATHWAY

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Thesis submitted for the Degree of Doctor of Philosophy

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May 1983

THE UNIVERSITY OF ASTON IN BIRMINGHAM

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SUMMARY

This project has been designed to study the visual effects of three conditions which produce a deterioration in vision with, in most instances, little or no fundus changes. These conditions are namely, 1) tobacco-alcohol amblyopia, 2) visual disturbances due to drugs used in tuberculotic therapy and 3) West Indian amblyopia.

For the first two conditions, two patient groups were studied. One group was composed of visually symptomatic patients who were suffering from the condition whilst the other group was composed of visually asymptomatic patients who were receiving the causative substance (for example, Ethambutol) on a chronic basis. The latter group acted as 1) a control for the affected group and 2) a group of patients who might demonstrate early visual changes.

The tests which have been used to examine these patients, consisted of a cross-section of objective electrophysiological and subjective psychophysical tests. They are as follows:

1) dark-adapted low-intensity and photopic electroretinograms,
2) transient visual evoked responses to flash and pattern stimulation,
3) visual field assessment using the Friedmann visual field analyser
4) determination of flicker fusion thresholds at three representative frequencies

and 5) assessment of visual acuity for distance and near

In the two groups of visually symptomless patients, it has been found that the most sensitive test in detecting subclinical changes is the visual evoked response. However, for the chronic alcoholic group, it is the foveal pattern stimulation which has produced the most significant results whilst for the tuberculotic group, it has been flash stimulation which has been most effective in monitoring visual changes during therapy.

For both the symptomatic and asymptomatic patients in all three conditions, visual disturbances have been observed at the retinal level although the results have indicated more marked changes occurring higher up the visual pathway. In the visually affected patients, all of the tests used, demonstrated abnormal changes in the visual system.

Key words: tobacco-alcohol amblyopia; Ethambutol; West Indian amblyopia; symptomatic; asymptomatic

DECLARATION

The accompanying dissertation entitled "The effect on visual electrophysiological and psychophysical investigations of substances primarily inducing a deleterious effect on the retinal ganglion cells and/or higher up the visual pathway" is submitted to the University of Aston in Birmingham in support for an application for the Degree of Doctor of Philosophy.

The dissertation is based on independent work by the candidate - all contributions from others have been acknowledged fully in the dissertation itself. The supervisors contributions were those normally made in a British College or University. None of the work described has been, or is being, submitted for any other Degree or Diploma to any other University.

I hereby declare that the statements in this declaration are true in all particulars.

D. Williams

ACKNOWLEDGEMENTS

I wish to extend my gratitude to Professor G F A Harding who undertook the task of being my supervisor and gave constant help and advice throughout the investigation. To Mr N Drasdo for his useful discussions and assistance on various aspects of my project. To Dr J Insley, Dr J Innes, Professor S J Crews and all the other physicians who made their patients available for participation in this investigation.

I am also very grateful to Mr R Clement for preparing the statistical programs, Ms T Powell for her graphical assistance, Mrs A Davies and Mrs M Geddes for typing the manuscript. Last, but not least, to my parents for their financial support.

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CHAPTER 1

INTRODUCTION TO THE PROJECT INCLUDING ITS OBJECTIVE.

INTRODUCTION TO THE PROJECT, INCLUDING ITS OBJECTIVE

It has long been known that certain substances have produced a "blurring of vision" with minimal or absent fundus abnormalities and without inducing any pain (Vaughn, 1617; Samelsohn, 1880). In the literature, the lists of substances producing affections of the optic nerve are quite lengthy; however on closer inspection, it is observed that most of the drugs bring about their chief damaging action on the intraocular layer of the retina or on some other structure of the eye. For example, Chloroquine is documented as causing retrobulbar neuritis, although it is known to have its major toxic effect on the pigmented areas of the eye (Harrington, 1971; Grant, 1974; Margach, 1976; Crews, 1977).

The purpose of this project is to study individuals who have received those substances and who are suffering from those conditions, which have been reported to cause a deterioration in vision, in most instances with little or no fundus changes and are thought to have their main initial harmful effect upon the retrobulbar sections of the optic nerve (Table1.1). The industrial chemicals will not be included in this study and it is the chronic rather than the acute effects of the listed substances and their associated conditions which are to be investigated.

The project is to adopt a particular format of investigations which will now be described. For each condition listed, there are two patient groups. One group consists of persons who actually have visual disturbances and are suffering from the condition, for example, Ethambutol toxicity, whereas the second group consists of

Condition	Causative Substance	Aetiology	Optic Neuritis	Retro-bulbar Neuritis	Fundus Changes	Colour Vision Changes	Visual Field Changes	Miscellaneous Affections	Therapy/ Diagnosis
Tobacco-alcohol amblyopia	Tobacco and/ or alcohol	Nutritional? Toxic?		X	Temporal pallor of optic disc sometimes develops.	Loss of sensitivity over whole spectrum.	Bilateral central or centrocaecal scotoma eventually extending to the periphery.	Possible disturbance of oculomotor system.	Vitamin B_{12} (hydroxocobalamin), methionine, improved diet and abstinence Some improvement often occurs within a few weeks or months.
Visual disturbances due to drugs used in treatment of Tuberculosis.	Ethambutol (Myambutol, Ebutol).	Toxic - Possible chelation of zinc by Ethambutol and Isoniazid thus making it unavailable for axoplasmic transport.	X	X	In the case of Ethambutol toxicity, fundus usually appears normal. However, optic neuritis & hyperaemia of disc have been seen; flame-shaped haemorrhages and dilatation of veins rarely seen; optic atrophy rarely develops.	Impaired colour vision especially to red and green.	Bilateral central or para-central scotoma and/or peripheral constriction; central bitemporal hemianopia has been reported.		After cessation of drugs, vision may become worse for the first month but it usually improves thereafter. Vitamin B_6 (pyridoxine) is sometimes used during administration of drugs although it is not known to aid recovery once visual impairment has occurred.
	Isoniazid		X	X	In the case of Isoniazid toxicity, in addition to optic neuritis, papilloedema & optic atrophy have been seen.			Peripheral polyneuritis is the main side effect of Isoniazid.	
West Indian Amblyopia	Bush teas? Cassava? Yams? General privation? Sunlight? Yaws?	Nutritional? Toxic? Race Related?		X	Temporal pallor of optic disc is often seen; pallor of entire disc has sometimes been reported.	Loss of sensitivity to red and green has been reported.	Bilateral central or para-central scotoma and/ or peripheral contraction.	Nerve deafness and peripheral neuritis have been reported in a few patients.	Vitamin B complex and vitamin B_{12} have been used but have produced disappointing results; the condition eventually becomes stable and does not lead to total blindness.

Table 1.1 TABLE SHOWING VISUAL DISTURBANCES CAUSED BY CONDITIONS TO BE STUDIED.

persons who are taking the causative substance/s on a chronic basis, for example, patients treated for tuberculosis. This group fulfils two roles, that is to act as 1) a control for the affected group and 2) a group of patients who may possibly show early changes in the visual tests to be used and if they do, what percentage of these patients reveals any changes. In addition to these two groups, a third group of clinically normal subjects is to be examined in order to establish normative data.

On referring to Table 1, it is seen that the three conditions to be studied are 1) tobacco-alcohol amblyopia 2) visual disturbances due to the drugs used in the treatment of tuberculosis and 3) West Indian amblyopia. The causative substances of the first condition have been reported as being tobacco or alcohol or a combination of them. There are some workers who believe that tobacco is the main cause of the disease and alcohol is an inconsistent factor (Traquair, 1934; Schepens, 1946; Freeman et al. 1958; Freeman and Heaton, 1961; Foulds et al. 1974; Bronte-Stewart et al. 1976) whilst others feel that alcohol amblyopia and tobacco amblyopia should be treated as two separate entities (Harrington, 1971; Reed and Drance, 1972). On the other hand, there are several workers who have maintained that the condition is caused by the combined effects of the two substances (although either substance on its own can have the same effect) since most heavy drinkers also smoke and vice versa (Jackson, 1914; Sichel, 1939; Carroll, 1944; Victor et al. 1960; Victor, 1963; Victor and Dreyfus, 1965; Duke-Elder, 1975; Dang, 1981).

It is for these reasons that it has been decided that a number of chronic alcoholics would be used for the control patient group who

consume both alcohol and tobacco on a continuous basis but are not known to possess any visual defects due to their effects. These alcoholics are patients of the "Alcoholic Addiction Unit" of one of the large city hospitals. The second group is made up of patients from the adjacent eye hospitals who have been diagnosed as suffering from tobacco-alcohol amblyopia.

The second condition which is listed in Table1.1, is due to the drugs used for the chemotherapy of tuberculosis. The persons who form this control patient group are from another of the large city hospitals and are undergoing treatment for tuberculosis. The drugs which are employed are Ethambutol, Isoniazid and Rifampicin mentioned in order of highest to lowest probability of causing ocular side effects. So far, Rifampicin has not been reported as giving rise to any ocular side effects (Grant, 1974; Martindale, 1977; Meyer and Hoigne, 1980). Since Ethambutol is the drug which is most likely to produce visual abnormalities, the investigatory procedure is arranged in relation to the administration of this drug. The affected patients have been diagnosed as having an ocular toxicity which is due to Ethambutol, sometimes in association with Isoniazid

For the third condition, West Indian amblyopia, only patients who are suffering from this disease are to be examined. The reasons for the omission of a control patient group is because it still remains obscure which substance/s are responsible for the development of this condition. Although this will be dealt with in more detail in the following chapter, many influencing factors have previously been suggested, for example, bush teas, cassava and bright sunlight, but none of these has been isolated as being the primary cause.

In order to carry out this investigation, certain psychophysical and electrophysiological tests are to be employed allowing a comparison to be made to determine the usefulness of different types of tests in the early detection of abnormal ocular changes. In addition to this, the clinical objective electrophysiological techniques are known to have added advantages, in that:-

1) they can be used to examine the visual function of non-communicative patients including young children and handicapped persons, persons who are unable to speak the language etc.
2) electrophysiological tests can be a beneficial aid in diagnosis where the ~~physiological~~ psychophysical results are dubious or unreliable. Nevertheless, it should be mentioned that an attention factor is also involved in electrophysiological testing (Galloway, 1981), although to a much less extent than in the psychophysical tests.
3) they complement the psychophysical tests in localizing which structure/s of the eye might be damaged.

There is one main disadvantage in performing electrophysiological tests and that is the time taken. Although the procedure seems to be time-consuming it should be realized that many types of stimulation (for example, changes in check and field sizes) can be used to examine various mechanisms of the visual system. If psychophysical tests were used to perform an equivalent function, it would take an even longer time, especially since patient participation is so important. Therefore electrophysiological tests demonstrate many advantages which outweigh their main disadvantage and this is

the reason for their continued popularity in many clinics.

The electrophysiological and psychophysical tests which have been chosen to be used in this project are as follows:-

A Electrophysiological Tests

1) Photopic and dark-adapted low intensity electro-retinograms (ERG).

2) Transient visual evoked responses (VER) to flash, pattern reversal and pattern appearance - dis-appearance stimulation, employing different check and field sizes, black/white and coloured stimulation.

B Pyschophysical Tests

3) Central visual fields (25^{o}) to white light, using the Friedmann Visual Field Analyser, Mark II. In addition to this, the macular thresholds to red, green, blue and white are to be determined.

4) To observe the changes in the thresholds to flicker modulation at three different frequencies, that is, a slow, a medium and a fast frequency.

5) Routine visual acuity assessment by the Snellen letter acuity chart and the 'N' series test type.

These tests have been selected as it is thought that they will provide a comprehensive examination of the type of visual defects which may occur with the substances given in Table 1.1. The variations in the visual signs and symptoms which may present with each condition will be described in more detail at a later stage.

CHAPTER 2

THE HISTORY AND DEVELOPMENT OF THE VISUAL STUDIES ON THE CAUSATIVE SUBSTANCES AND THEIR ASSOCIATED CONDITIONS.

THE HISTORY AND DEVELOPMENT OF THE VISUAL STUDIES ON THE CAUSATIVE SUBSTANCES AND THEIR ASSOCIATED CONDITIONS

2.1 TOBACCO AND ALCOHOL

2.1.1 The General Effects of Alcohol and Tobacco on Society

In this section it is intended to present the studies on the visual changes caused by alcohol ingestion. However, before doing this, a brief account will be given on the general effects of these substances on society as they influence the daily lives of many individuals to a large extent. This account will include the proposed reasons for addictive behaviour, the definition of the term "alcoholism" and the effects of alcohol and tobacco on the human body.

Both alcohol and tobacco are readily available and unfortunately some users are unable to control their consumption of these substances. Dole (1980) refers to this as addictive behaviour for which there is no rational explanation. He listed the several theories which have been proposed to explain the reasons for addictive behaviour but which all have their pitfalls. These are as follows:-

1) The older theory that addiction is due to an addictive type personality. This theory fails to satisfy the reasons for the specificity of addiction, for example, why do alcoholics prefer alcohol to other substances.
2) That an addict continues to take drugs because he is afraid of the symptoms of withdrawal which compels him to obtain relief in another dose. However, this theory does not explain why addicts relapse after "detoxification".

3) That addiction is equated with physical dependence which is an adaptive consequence of taking certain chemicals repeatedly. However, with this theory, a relapse should not occur after individuals have been "detoxified" but they do in many instances. Dole points out that this brings out the distinction between dependence and addiction. In order to reconcile this difference, some workers introduced the concept of psychological dependence but then this can only be concluded from the type of behaviour which it seeks to explain.

4) An alternative psychopharmacological theory identified a relapse with conditional responses, for example when an alcoholic returns to his old environment, it triggers off a relapse. A sociopsychological theory which continues on from this explains addiction as being a means of escape from an oppressive environment, for example, poverty.

Dole points out that addiction to alcohol and smoking affects all strata of society and not until the underlying biological factors causing addiction are understood can any progress be made in instituting worthwhile progress to prevent the problem. He proposed that "the addict has delivered to his nervous system, a pharmacological hammer blow which is followed by a rapid withdrawal which sensitizes him for the next dose".

It has also been suggested that genetic considerations are an influencing factor in the onset of alcoholism. Goodwin (1976) and a study performed by the Royal College of Psychiatrists (Alcohol and Alcoholism, 1979) reported that there was a significantly higher likelihood of first degree male relatives of alcoholics developing a drinking problem than those of non-alcoholics. Although this could be partly attributed to

parental influence as well as genetic processes, support for the latter proposition comes from Goodwins study when the sons of alcoholics who were adopted from their original homes in early life were observed. However, in another study, fostered children of alcoholic fathers who had left their original homes at 10 years old, were compared to a control group of fostered children of non-alcoholic fathers. At 30 years old, no difference was found between these two groups in their adult drinking behaviour (Roe , 1949).

What is meant by the term "alcoholism" has created some confusion because it has been defined in various manners by different workers. Edwards et al. (1977) realised this and endeavoured to differentiate between "the alcohol dependency syndrome" and "alcohol related disabilities". The alcohol dependency syndrome is described as "a state, psychic and usually also physical, resulting from taking alcohol characterised by behavioural and other responses that always include a compulsion to take alcohol on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid the discomfort of its absence; tolerance may or may not be present". (page 33). Alcohol related disabilities were described as "the mental, physical or social harm associated with drinking". The report in "Alcohol and Alcoholism" (1979) mentioned that for most people "alcoholism" is possibly synonymous with the alcohol dependency syndrome or the disease of alcoholism, which is possibly its usage by "Alcoholics Anonymous".

Although it is possible to place some heavy drinkers into one of the categories described by Edwards et al. (1977), in many cases there is a co-existence of the states described in the two categories. This is probably the case for the alcoholic population which is to be studied

in this project, that is, they have a craving for alcohol with a possibility of incurring serious or persistent disabilities.

Alcoholism is known to lead to sociological, mental and physical complications, for example, the relationship between the alcoholic and all the people with whom he comes in contact, is affected. The risk of dying is increased by two to three times more than the general population of the same age and sex. From 1950 to 1976, the alcoholic consumption per head of adult population has gone up by 74% (Alcohol, 1981).

The Effect of Alcohol on the Human Body

Alcohol is metabolised almost completely into carbon dioxide and water, with only a small percentage excreted unchanged in the breath and urine (Marks, 1979). If a strong drink is taken it goes into the circulation without much delay because it is absorbed from the stomach and intestines quickly and passes through the liver rapidly. (Dole, 1980).

In many instances, both alcoholics and smokers neglect their diets and consequently suffer from nutritional deficiencies and an increased susceptibility to other infections. Malnourished and fasting individuals with already depleted hepatic glycogen stores, who continue to imbibe moderate to large amounts of alcohol, might lower their blood glucose concentrations to such an extent as to impair brain function and even its structural integrity (Marks, 1979). Lusins and Zimberg (1980) used the CT Scan to investigate cerebral atrophy in 50 chronic alcoholics.

58% of the patients demonstrated some degree of cerebral atrophy and a significant difference was found in the duration of problem drinking between patients with normal and abnormal CT scans (that is, 8.7 yr. versus 13.3 yr.). However, no correlation was observed between the CT scan results and age of onset of drinking and age of the patient. Another study on chronic alcoholics without liver disease, also showed significantly more cerebral atrophy on the CT scan than in age-matched controls. It was suggested that many cerebral effects of alcoholism resemble a state of accelerating age (Carlen, et al. 1981).

However, it still remains uncertain why many persons who have "drunk" heavily for many years do not develop brain damage whilst occasionally a young moderate drinker becomes a casualty although his diet seems to be adequate. This would suggest that individuals have different tolerance thresholds to alcohol or perhaps some additional factor contributes to the illness, for example, stress.

Alcohol can have a toxic effect on other body tissues, for instance, the liver. Deaths from cirrhosis of the liver went up from 23 death rates per million in 1950 to 37 per million in 1975 (Alcohol and Alcoholism, 1979). Inflammation and enlargement of the liver, stomach and duodenal ulcers may also occur. There is also the risk of Korsakoffs psychosis developing which is an amnestic syndrome that follows delirium tremens and toxic states. It is often seen associated with a nutritional deficiency in alcoholism. The disorder results from damage to the medial aspects of both temporal lobes. In alcoholism, the destruction is usually irreversible and the prognosis

is poor (Hillyard et al. 1980). Inflammation of the nerves which supply the limbs (peripheral neuritis) might also occur in heavy drinkers. In pregnant female alcoholics, developmental damage to the foetus might take place (Hrbek et al. 1980; Borges and Lewis, 1981).

Data obtained from admissions to mental illness hospitals showed that rates per 100,000 of the population with a primary diagnosis of alcoholic psychosis or alcoholism increased from 18.6 to 38.6 in males and from 4.6 to 15.3 in females between 1964 and 1977. The greatest increase took place in the 25-64 age groups (Mental Health Enquiry, 1980).

There are two other rare conditions which should be mentioned which selectively affect the myelin sheath and are frequently but not exclusively associated with chronic alcoholism. They are 1) the Marchiafava-Bignami Disease and 2) central pontine myelinosis.

The Effects of Tobacco Smoking

Tobacco smoking, whether in the form of cigarettes, cigars or pipe tobacco, has created concern because of its effects on health. The smoke is a mixture of gases and minute tarry droplets in which nearly 1000 compounds have been identified (Stedman, 1968). Its composition varies according to the type of tobacco plant, the way that it is cured and the way it is smoked. The main stream smoke is faintly acid in most cigarettes and is less irritant than that of pipes which may be acid or alkaline, or than cigar smoke which is alkaline.

Some of the compounds in tobacco smoke act chiefly in the mouth, air passages or air sacs of the lungs where they are deposited, whilst others are absorbed into the blood and may act upon the body tissues. The substances which have gained medical importance fall into four main groups, that is, 1) nicotine, 2) carbon monoxide (CO) and other gases 3) known cancer-producing substances and 4) irritant substances.

1) Nicotine - the most notable action of nicotine involves a direct effect on sympathetic and parasympathetic ganglion cells which usually occurs as a transient excitation followed by depression. It is known to mimic the action of acetylcholine and noradrenaline which are the chemical neurotransmitters released at nerve endings for the transmission of impulses. The predominant effects are central stimulation and/or tranquilisation, transient deep breathing (hyperpnea), peripheral vasoconstriction usually causing an increase in systolic pressure, supression of appetite, stimulation of peristalsis and with larger doses, nausea.

Cigarette smokers are said to inhale and absorb about three times as much nicotine as cigar and pipe smokers and with each puff, about 0.1 mg given intravenously, is absorbed. (Smoking and Health Now, 1971).

2) CO and Other Gases - CO occurs in high concentration in cigarette smoke and its average concentration in smoke inhaled into the lung is approximately 400 parts per 1,000,000. It has a greater affinity for haemoglobin than oxygen and consequently there is a loss

of up to 10% of the capacity of the blood of smokers to transport oxygen. The heart muscles have a great demand for oxygen and if atheroma (CO has been shown to increase its formation) is already present, then CO further interferes with their blood supply. In addition to this, the action of cyanates (derived from hydrogen cyanate in tobacco smoke) on the metabolism of the heart could impair the efficiency with which it uses oxygen. The level of CO has been found to be higher in cigarette smoke than in pipe and cigar smoke (Smoking and Health Now, 1971).

3) Known cancer-producing substances - Filtered cigarettes have been developed which selectively remove some cancer initiators or promoters from smoke. The addition of certain chemicals, such as nitrates which make the tobacco burn more quickly, reduces the amount of condensation from the tobacco and renders it less carcinogenic (Smoking and Health Now, 1971; Smoking and Health, 1979). Although pipe and cigar smoke is less liable than cigarette smoke to cause lung cancer, the smoke from cigars and pipes is more liable to cause cancer of the skin (Smoking and Health Now, 1971).

4) Irritant Substances - These substances (which are less irritant in cigarette smoke) are responsible for a) the immediate coughing and narrowing of the bronchial tubes following inhalation, b) arresting the beating of the cilia and c) stimulating bronchial glands to secrete increased amounts of mucus. This may contribute to the causes of pulmonary disease, for example emphysema, by interfering with the self-cleansing mechanism of the lung. The bronchial reaction is reduced by filters which remove either the particle or vapour phases of the smoke. Some of these irritants are also co-carcinogens.

It can be seen from the above account, that smoking is a possible contributor to the development of heart disease, cancer, especially of the lungs and pulmonary disease. However, this depends on the depth of inhalation, the rate of smoking, the length of cigarette smoked, the number of puffs taken, the length of time the cigarette is held in the mouth, the age of onset of smoking and the type of tobacco smoked.

Coronary heart disease has become a leading cause of death in developed countries and from studies carried out, it has been shown that the risk of dying from heart disease is greater among cigarette smokers than in non-smokers and smokers of pipes or cigars. The risk is about three times that of non-smokers under 55 (being greater in men) and only one and a half times at older ages.

Investigations in ten countries, including Britain, have shown that when previous smoking habits of patients with lung cancer are analysed, there are many more heavy smokers and fewer light and non-smokers among patients of the same sex, age and place of residence without lung cancer. These studies also suggest a link between the number of cigarettes smoked and the incidence of the disease. Cancers of the mouth, pharynx, larynx and the oesophagus may also occur (Smoking and Health Now, 1971).

It has been reported that the greatly increased risk of illness and death from chronic bronchitis and emphysema in smokers is due to their exposure to smoke rather than to any constitutional factor that might cause both liability to chest disease and an increased

desire to smoke cigarettes (Smoking and Health Now, 1971; Smoking and Health, 1979).

Like alcohol it has been suggested that the extra risk of cigarette smokers in developing heart disease and lung cancer may not be due to their smoking but to their inheriting both a desire to smoke and a liability to these diseases. However, if hereditary was responsible for the increased risks of smokers, then this would be unaffected by giving up smoking. After ten years of abstinence, the risk is close to that of non-smokers although the risk in ex-heavy smokers continues to be raised (Doll and Hill, 1964; Hammond, 1966).

Smoking, like alcohol, affects the development of the foetus, increases the risk of duodenal and peptic ulcers and tuberculosis of the lungs. (Smoking and Health Now, 1971; Smoking and Health, 1979).

Now that a brief mention has been made of the general environmental, physical and mental effects of alcohol and tobacco it would be appropriate to continue this section with a historical account of the effects of these substances on the visual pathways and then go on to the more recent studies in this subject.

2.1.2. Historical Review of the Studies Relating to the Effects of Tobacco and Alcohol on the Visual Pathways

The tobacco plant was used by the Indians in the Americas for its great healing powers long before it was introduced to Europe by Fernandes in 1558. It was adopted as a remedy for all diseases and

gradually entered the royal courts; however, severe objections broke out in the 17th century on the physical and moral effects of tobacco.

In 1617, a Dr Vaughan was the first to refer to its harmful effects on vision, mentioning in his report that "it dims the vision". However, people continued to use it but more for its pleasurable values rather than for its remedial values.

Beer (1792) explained the reasons for this amaurosis caused by tobacco as being due to the loss of fluid in the copious spitting of tobacco smokers and in the loss of nasal mucus in the snuffing of tobacco. Later in 1833, Mackenzie published a textbook which included the possibility of amaurosis occurring with the use of the highly deleterious poison, tobacco.

Sichel (1863) felt that most people could not tolerate more than 20 gm/day without seriously affecting the vision. Hutchinson in the same year, produced an article on 64 patients with tobacco amblyopia several years after he first saw them and found that 75% of his patients recovered. He thought that recovery was possible if smoking was stopped and the blindness was not present for too long. He noticed that those who did not recover, smoked the cheapest uncured type of tobacco. However, he could not understand how heavy smokers in certain parts of the world (such as Turkey, Egypt, etc.) did not develop this condition. Carter (1864) and DeSchweinitz (1896) also observed this and they explained it by saying that the tobacco used in these parts of the world was less potent in nicotine than that used in the USA and Europe. Perhaps the condition was not yet recognised in

these countries and therefore it was not reported. De Schweinitz felt that other factors which favoured the deleterious effect of tobacco on vision were alcohol and malnutrition from any source. In the autopsy of one case, he found degeneration of the papillo-macular bundle. Schepens (1946) also postulated that tobacco amblyopia is a deficiency disease since he found an increase of amblyopia in Belgium where undernourished people smoked green tobacco during the second world war.

Before any reference is made to the controversy between investigators as to whether tobacco amblyopia and alcohol amblyopia should be classed as two separate entities or a single entity, a short review on the effects of alcohol on vision will be given.

It seems as if the first reference to the affection of vision by alcohol was in 350 BC by Aristotle, the Greek Philosopher who stated that "anyone who became blind from his drunkeness or other indulgencies would be blamed by everyone but anyone who became blind by no fault of his own, would not be reproached by anyone". It does not appear that alcohol amblyopia was again mentioned until 1749 when Boerhaave wrote of a patient who lost his sight after drinking large quantities of wine; however he regained it after abstinence from alcohol.

Sichel (1837) who later reported on tobacco amblyopia in 1865, distinguished between acute and chronic alcoholism and commented on the blindness resulting from the latter. He advised one of his patients who recovered, to abstain from liqours, coffees and spices, drinking only weak diluted beer or wine and to have a balanced diet. Horner

(1878), Forster (1880) and Sachs (1889) also felt that malnutrition was a contributing factor in the genesis of alcohol-tobacco amblyopia.

After developing the first perimeter, Forster (1880) detected centrocaecal scotomata in alcohol amblyopia and he assumed that it was due to an optic nerve lesion rather than a retinal lesion. To provide evidence for Forster's assumption, Samelsohn (1880), Uthoff (1888) and Sachs (1889) carried out autopsies on chronic alcoholics (some of whom never used tobacco) and found degeneration of the papillomacular bundle in the region of the optic nerve. On the other hand, Friedenwald (1901) found that the retinal ganglion cells were primarily affected with the destruction of the optic nerve and fibrosis occurring afterwards.

In his study, Uthoff (1888) also distinguished between retrobulbar neuritis and toxic amblyopia which made a notable contribution to ophthalmic literature. He described the former condition as occurring in younger patients with a scotoma which is central, absolute and usually unilateral. It is of sudden onset accompanied by pain on eye movement. In toxic amblyopia, the condition is bilateral with a less severe onset. There is a relative centrocaecal scotoma, more pronounced for red and green targets than for white targets.

Wood (1892) published some articles which discussed alcohol and tobacco as causes of toxic amblyopia. Although he had no proof, he suggested that the impurities or the additives in alcohol and tobacco could be the genuine cause for example, fused oil in alcohol and nicotine in tobacco. He also thought that there was an underlying nutritional factor.

Until this time, only men were reported to develop tobacco-alcohol amblyopia, however Chisholm (1887) commented on two cultured ladies who had the symptoms of toxic amblyopia of which both smoked heavily but only one drank alcoholic beverages. The vision of one of the ladies improved on abstinence and treatment with strychnine but the other lady never returned.

The question as to whether tobacco amblyopia and alcohol amblyopia should be treated as two single entities or as one combined entity has been a point for debate for a long time. At a meeting of the Ophthalmological Society of the UK which discussed this topic, it was indicated that tobacco was the substance of aetiological importance in the development of toxic amblyopia. It was also suggested that no-one had ever seen amblyopia in an alcoholic who did not smoke as well (Nettleship, 1887). This was supported by ophthalmologists such as Nettleship, Eales and Gunn (Dunphy, 1969). However, Fuchs (1883), Horner, (1878), Connor (1890), Jackson (1914) and other ophthalmologists insisted that toxic amblyopia was caused by a combination of alcohol and tobacco, although either substance on its own could cause the condition.

Hirschburg (1879) stated that he could distinguish between tobacco amblyopia and alcohol amblyopia by the type of scotoma but Uthoff (1888) and De Schweinitz (1896) could not justify this difference.

2.1.3. Development of the Studies on Tobacco-Alcohol Amblyopia including those on the Chronic Administration of Tobacco and Alcohol.

a) Psychophysical Studies

The incidence of tobacco-alcohol amblyopia in patients seen at Eye Hospitals or elsewhere remains vague. However, there have been reports that the occurrence of this disease, or at least tobacco amblyopia has decreased over the years although the consumption of tobacco and alcohol has increased (Harrington, 1971; Grant, 1974; Smoking and Health, 1979; Alcohol and Alcoholism, 1979). Perhaps this is due to the stricter regulations imposed in the refinement of these two products.

Recently, Bronte-Stewart et al. (1976), claimed that about 30 new cases are referred to their ophthalmological clinic in Glasgow per year who satisfy their diagnostic criteria for this disease. This would indicate that although this condition might not be as prevalent as before or as prevalent as other ocular diseases, it still exists as a recognisable problem and therefore would warrant any research which could lead to its early diagnosis.

The signs which have been associated with tobacco-amblyopia are as follows:-

1) a gradual bilateral decrease in central vision with one eye being usually more affected than the other. The patient usually presents with a visual acuity (VA) of 6/18 or worse.

2) bilateral centrocaecal or central scotomata extending to the periphery with time. The defect often goes well beyond fixation and its density varies within the centrocaecal area (Figure 2.1, 2.2).

3) this is accompanied by a decrease in colour discrimination over the whole spectrum.

4) The fundus does not show any pathology in most cases although temporal pallor of the optic disc has been reported.

As already mentioned, certain workers such as Hirschburg (1878), Harrington (1971) and Reed and Drance (1972) claimed that they could identify tobacco amblyopia and alcohol amblyopia (they believed that amblyopia associated with chronic alcoholism is a nutrition deficiency amblyopia and does not exist on a toxic basis like tobacco amblyopia) separately by their visual defects where as other workers such as De Schweinitz (1896); Carroll (1944); Victor et al. (1960); Victor 1963; Victor and Dreyfus (1965) and Duke-Elder (1975) were unable to do so. Whereas the latter set of workers found either central or centrocaecal defects, the former set of workers reported that alcohol amblyopia produces central scotomata whilst tobacco amblyopia produces centrocaecal scotomata. Using the Bjerrum screen, Harrington (1971) stated that in tobacco amblyopia the scotoma may either develop mid-way between the blind spot and the fixation spot and extend on both sides, or it may develop from the blind spot and extent nasally towards the fixation point. The density of the scotomata is hardly uniform. In the case of alcohol amblyopia, the scotoma is a central one which is usually slightly irregular in shape and varies in size from 2^{o} to 5^{o} and may extend temporally to form a centrocaecal defect. The density of the scotoma is relatively uniform.

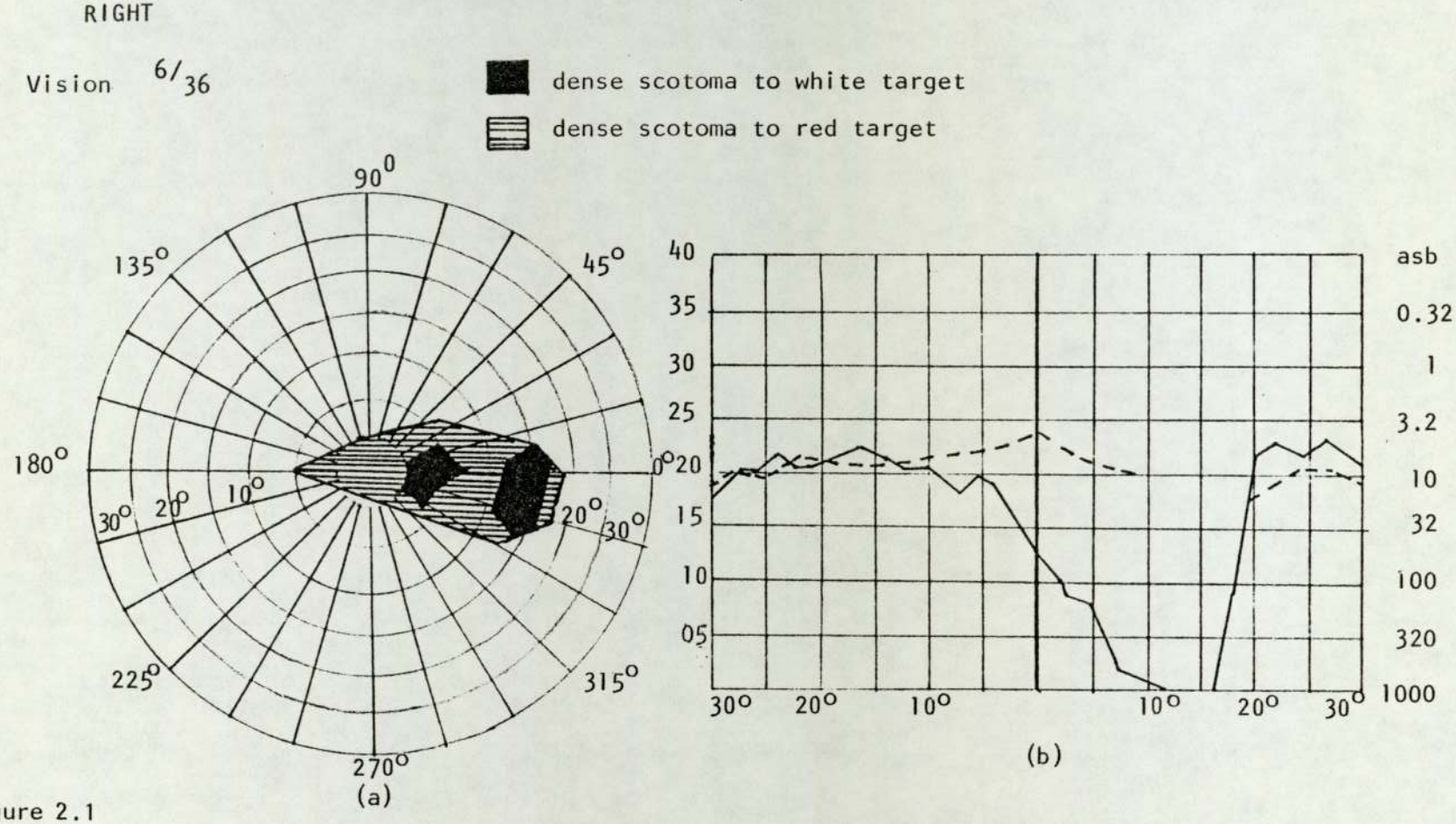


Figure 2.1

(a) Diagram showing a centrocaecal scotoma of relatively uniform slope to small white & red targets (0.4=17')
in a tobacco-alcohol amblyope (using the Tubinger perimeter)

(b) Corresponding static curve along the 0-180° meridian showing the sloping defect (Broken line is a mean curve from 10 eyes in age group 60-75 years)

(After Wilson and Reid, 1969)

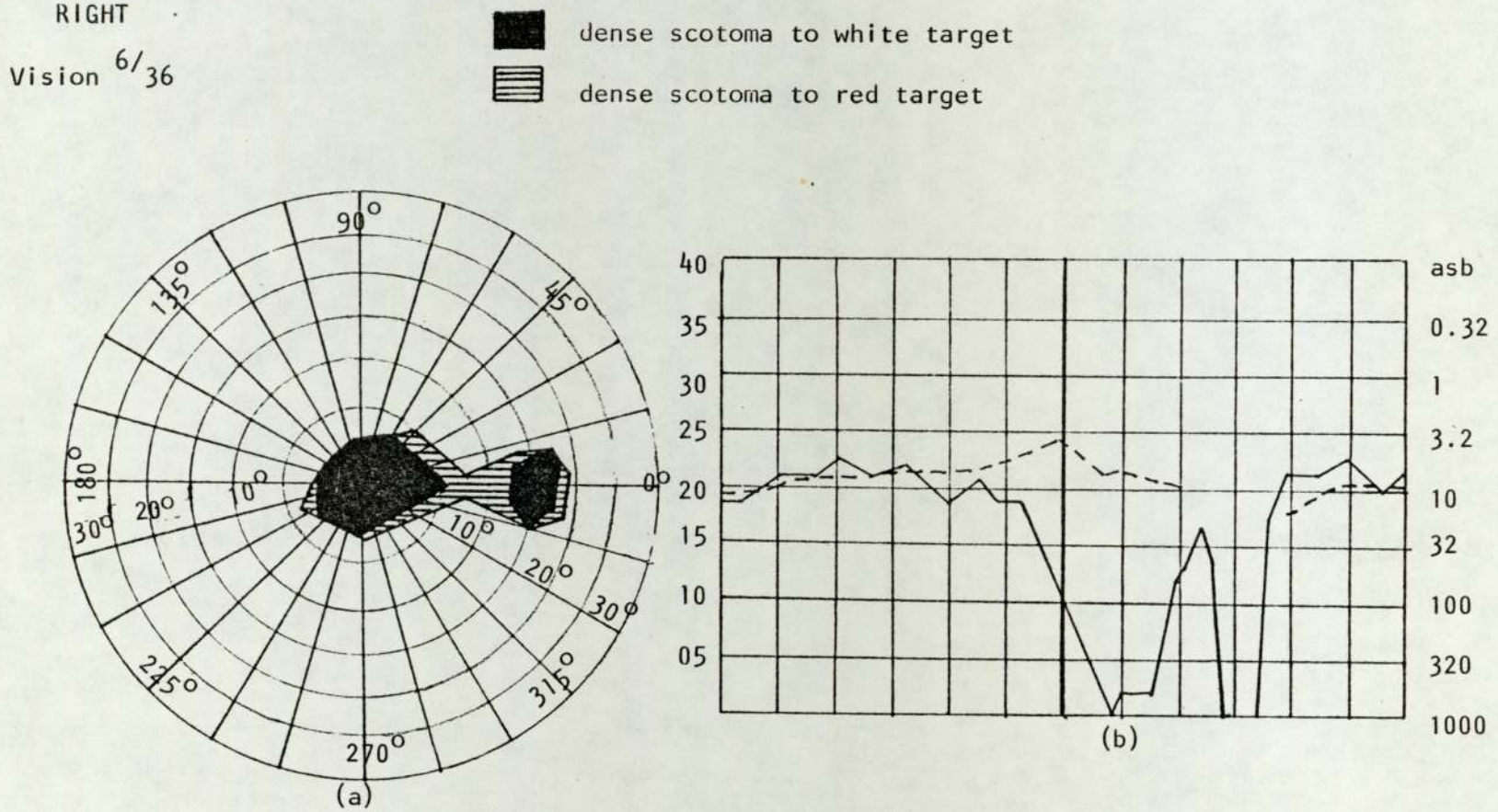


Figure 2.2 (a) Diagram showing a centrocaecal scotoma interrupted by a notch to small white and red targets (0.4 = 17') in a tobacco-alcohol amblyope (using the Tubinger perimeter);

(b) Corresponding static curve along the 0 - 180° meridian, showing the spike defect (Broken line is a mean curve from 10 eyes in age group 60-75 years)

(After Wilson and Reid, 1969).

Zingirian and Riviara (1965) and Wilson and Reid (1969) employed a static method to determine the light threshold of a small white target along the 0^{o} - 180^{o} meridian in 30 and 12 tobacco-alcohol amblyopes respectively. The target was presented at 2^{o} and 1^{o} intervals respectively within the central 30^{o} using the Tubinger perimeter and a tangent screen projection campimeter. The two studies reported bilateral centrocaecal scotoma of 1) a sloping type, which formed a regular slope between the blind spot and fixation spot (or beyond the fixation spot), and 2) a spiked type, which was more common and demonstrated a similar slope but was interrupted by a notch or notches in the centrocaecal area (Figure 2.1, 2.2).

Wilson and Reid (1969) stated that the recovery of VA depended on whether the central area increased more rapidly than the rest of the centrocaecal area. They also observed that 6 patients with improved VA's of 6/9 or better still revealed centrocaecal defects. Zingirian and Riviara (1965) found that the peripheral fields remained intact.

Friedmann (1970) examined the central visual fields (25^{o}) in the toxic and nutritional optic neuropathies using the Friedmann visual field analyser which also employs static campimetry. In his study, he included 2 cases of tobacco amblyopia, one being a heavy pipe smoker and the other a heavy cigar/pipe/cigarette smoker. He found a combination of central, centrocaecal and paracentral defects in the 2 subjects. There was a complete recovery in the field defect and VA in the subject with the less dense defect whilst there was only partial improvement in the other subject.

On comparing 6 patients with a vitamin B_{12} deficiency combined with tobacco-alcohol misuse, to 5 patients with only a B_{12} deficiency, Aulhorn (1977) observed that in the former case, both centrocaecal and central scotomata were seen whereas in the latter case, small round scotomata without centrocaecal character were seen. This worker postulated that the site of damage in the optic nerve is different for these two conditions.

Many investigators have found a reduction in colour discrimination in tobacco-alcohol amblyopes and also in chronic alcoholics. Galezowski (1883) was the first person to report the subjective colour defect of tobacco amblyopia. Francois and Verriest (1961) employed the Farnsworth Munsell (FM) 100 hue test and the Panel D-15 test to examine the colour vision in subjects with a variety of diseases. In tobacco-alcohol intoxication they found defects without a prominent axis. From their overall results they supported Koellners law that lesions in the deeper layers of the retina demonstrate a reduction in the blue/yellow region whilst lesions in the ganglion layers and in the optic nerve demonstrate a reduction in the red/green region. Therefore retinal and retrobulbar lesions would be indicated in tobacco-alcohol amblyopia.

Chisholm et al (1970) and Ainley (1970) used the FM 100 hue test on 65 and 15 patients respectively suffering from tobacco-alcohol amblyopia who were mostly pipe smokers. Besides finding a depression in colour discrimination in most regions of the spectrum with a predominantly red/green loss, which improved with treatment (from 1 - 9 months), they also observed that colour discrimination was

affected before VA and remained affected after VA had returned to normal levels. The former workers found a low but significant relationship between distance VA and the FM error score.

Bhargava and Phillips (1974) investigated the foveal thresholds to red, green and blue light in 12 tobacco amblyopes and in 12 age-matched controls. Their results showed the greatest significant difference between the groups for red stimulation with less significance for green and no significance for blue. From the results of this experiment and from those of Marre and Marre (1972), these workers felt that the lesion could be at the retinal level. Marre and Marre found that in retinal diseases the reduction of the sensitivity of the fovea increased with longer wavelengths but in optic nerve diseases, the reduction of the foveal sensitivity is constant over the whole spectrum.

Zisman et al (1978) measured the spectral sensitivity of a tobacco amblyope to a 1^{o} spectral test spot flickered at 1 and 25 Hz upon a bright white background. At both frequencies the overall spectral sensitivity was depressed especially at 1Hz. At 1Hz, the curve changed shape from a three-peaked to a broad single peak near 560 mm. There was a predominant depression at the blue end and a lesser depression at the red end. These workers concluded that the colour opponent and luminance responses may be directly related to Gouras-tonic and phasic cells.

There have been many studies performed to examine the colour vision of chronic alcoholics. Different workers have put forward that the

defect is of 1) the red-green type (Sakuma, 1973), 2) blue-yellow type (Cruz-Coke and Varela, 1965 and 1966; Sassoon et al. 1970; Ugarte et al. 1970), 3) either type or a dyschromatopsia without a predominant axis (Smith, 1971; Smith and Layden, 1971; Swinson, 1972; Verriest et al. 1980). A genetic predisposition to this disease has been suggested (Varela et al. 1969; Cruz-Coke, 1972) but this hypothesis has been questioned by other workers whose results fail to show any such tendency (Fialkow et al. 1966; Gorrell, 1967; Thuline, 1967; Smith, 1971; Smith and Layden, 1971; Swinson, 1972).

Cruz-Coke and Varela (1965) reported a high incidence of colour vision defects in alcoholics using the HRR pseudoisochromatic plates which only test red/green discrimination. Cruz-Coke and Varela (1966) and Varela et al. (1969) subsequently observed a high incidence of errors made on the HRR plates and FM 100 hue test (which were identified as lying along the blue/yellow axis in the latter test) in non-alcoholic female first degree relatives of alcoholics than in the female controls. Non-alcoholic male relatives demonstrated colour discrimination which was between that of the controls and male alcoholics. To these workers, the high incidence of colour defects in the alcoholics and their relatives indicated a genetic disposition whereby it was transmitted by the female on the X-chromosome. Fialkow et al. (1966) pointed out that the relatively high frequency of colour vision abnormalities in females argues against classic X-linked recessive inheritance.

Ugarte et al. (1970) and Sassoon et al. (1970) used the FM 100 hue test and further confirmed a high prevalence of blue/yellow defects amongst alcoholics. However, Fialkow et al. (1966) and Edwards (1970) criticised the studies of Cruz-Coke and his colleagues on the basis

of failing to retest their subjects to observe any changes over time, failing to define their criteria for alcoholism, poor selection of controls and inappropriate interpretation of their results.

Smith (1971) looked at the colour discrimination of large populations of alcoholics on the Ishihara and FM 100 hue tests (in order to compare his results with those of Varela et al. 1969). With both tests, he observed that the colour deficiencies improved with time in most patients and the incidence of major errors was about the same as that for the general population indicating that the colour defects were secondary to alcoholism and cirrhosis. In a subsequent study, Smith found that with the FM 100 hue test, instead of finding a predominantly red/green deficiency as was seen with the Ishihara plates there was a general decrease in all colour spectra. The occurrence of blue/yellow defects was not greater than that for red/green defects (also Smith and Layden, 1971). Like Smith, Fialkow et al (1966), Thuline, (1967) and Swinson (1972) also concluded that the colour defects are more likely to be acquired rather than of a genetic origin in alcoholism and cirrhosis. In the case of Fialkow and his co-workers, there was an improvement in the colour vision of their patients on re-testing and in the case of Swinson, there was practically no difference between the incidence of colour abnormalities in male and female alcoholics which is opposed to the hypothesis of any sex-linked genetic factor being responsible. Nevertheless, Swinson observed a higher percentage of colour defects in alcoholics than in the general population. This could be because he used a more comprehensive range of tests to examine the colour vision of his patients, that is the Ishihara and Dvorine plates and the Crawford anomaloscope. Swinson as well as Smith suggested that a nutritional factor was involved.

In 1980, Verriest et al. carried out a colour vision study on 38 alcoholics (9 out of 10 smoked) who were being "detoxified" in hospital. These investigators employed the Ishihara test, the Nagel anomaloscope, the Panel D-15 test and the FM 100 hue test. They found that on a whole about 50% of the results were abnormal in all the tests. Subjects who had abstained for less than 2 weeks showed a greater defect in all the tests but those who had abstained for more than two weeks seemed more deficient in the red/green region. Although the results of the various tests were contradictory when the influence of hepatic conditions were considered, the results of the FM 100 hue test showed that in hepatic patients, the blue/yellow discrimination was more affected whilst in the non-hepatic patients the red/green discrimination was more affected. This would suggest that if there is a persisting blue/yellow defect, then this could be linked with liver damage. Cruz-Coke (1965) had earlier reported that there was a highly significant association between colour vision defects and cirrhosis which was later linked to alcoholism (Cruz-Coke and Varela, 1965). However, Gorrell (1967); Reid et al. (1968) failed to find any increased incidence of colour defects in cirrhotic patients using the Ishihara, HRR and Dvorine plates.

With the exception of the study of Verriest et al. (1980), it is to be assumed that the VA of the alcoholic subjects in the other studies was not markedly affected as this parameter was not given. Verriest et al. excluded any alcoholics with a VA of less than 5/10 which would indicate that some of their subjects might have been suffering from tobacco-alcohol amblyopia. It can also be seen that conflicting results were obtained by various workers which could be due to the

different types of tests employed, the varying periods during or after hospitalisation at which the alcoholic patients were tested in each study and the differences or lack in defining the term "alcoholism".

2.1.3b Electrophysiological Studies

Over the past decade or so, increasing numbers of investigators have become interested in the influence of alcohol and smoking on electrophysiological tests. This interest has flourished not only because the use of these substances is so prevalent in our society but also because it is hoped that these tests will provide some useful physiological and clinical information, especially in detecting early changes in tobacco-alcohol amblyopia. First, the electrophysiological studies devoted to tobacco-alcohol amblyopia will be presented.

Stangos et al. (1970) and Stangos et al. (1977) carried out photopic and scotopic ERGs to white and red stimulation in patients with various ocular diseases. In the patients with tobacco-alcohol amblyopia and vascular diseases they found a decrease or abolition of the OPs to both stimuli. The disappearance of the OPs in patients with vascular diseases, especially diabetes was reported by other workers, indicating that it is affected by circulatory defects (Yonemura 1962; Yonemura et al. 1962; Simonsen 1968; Ikeda and Friedmann 1972; Ikeda 1976). However these workers did not say whether this is the case in tobacco amblyopia.

In 1976 Halliday reported on a 58 year old man with high tobacco and alcohol consumption who showed "scotomatous" visual evoked responses (VER)

to pattern reversal checkerboard stimulation (50'). He observed that the normal major positive component (P100) from the midline occipital electrode was replaced by a negative component which formed part of a triphasic PNP complex (positive, negative, positive complex, Figure 2.3).

In normal subjects, with half field stimulation it was shown that the major positive component appeared at the midline and ipsilateral electrodes (placed 5 cm. apart, on a line 5 cm. above the inion) whilst electrodes over the contralateral hemisphere picked up a triphasic PNP complex. By occluding the central region in healthy subjects, it was found that the normal positivity became very attenuated with the negativity being clearly visible which is the reason given for patients with central scotomata, for example, toxic amblyopes demonstrating this negativity rather than a positivity (Blumhardt et al. 1978; Kriss and Halliday, 1980).

Kriss et al. (1982) performed VERs to flash and pattern reversal stimulation (50') on 24 patients with a diagnosis of toxic neuropathy. Ninety-two per cent of the patients drank more than half a bottle of spirits or 4 pints of beer per day; 71% smoked more than 1/3rd oz. of tobacco or 40 cigarettes per day and 63% both drank and smoked. All patients had reduced VA's, colour defects, central or centrocaecal scotomata with disc pallor present in 68% of the patients. There was a general amelioration in the visual condition of most of the 13 patients who returned for subsequent studies after vitamin B_{12} therapy, abstinence and time.

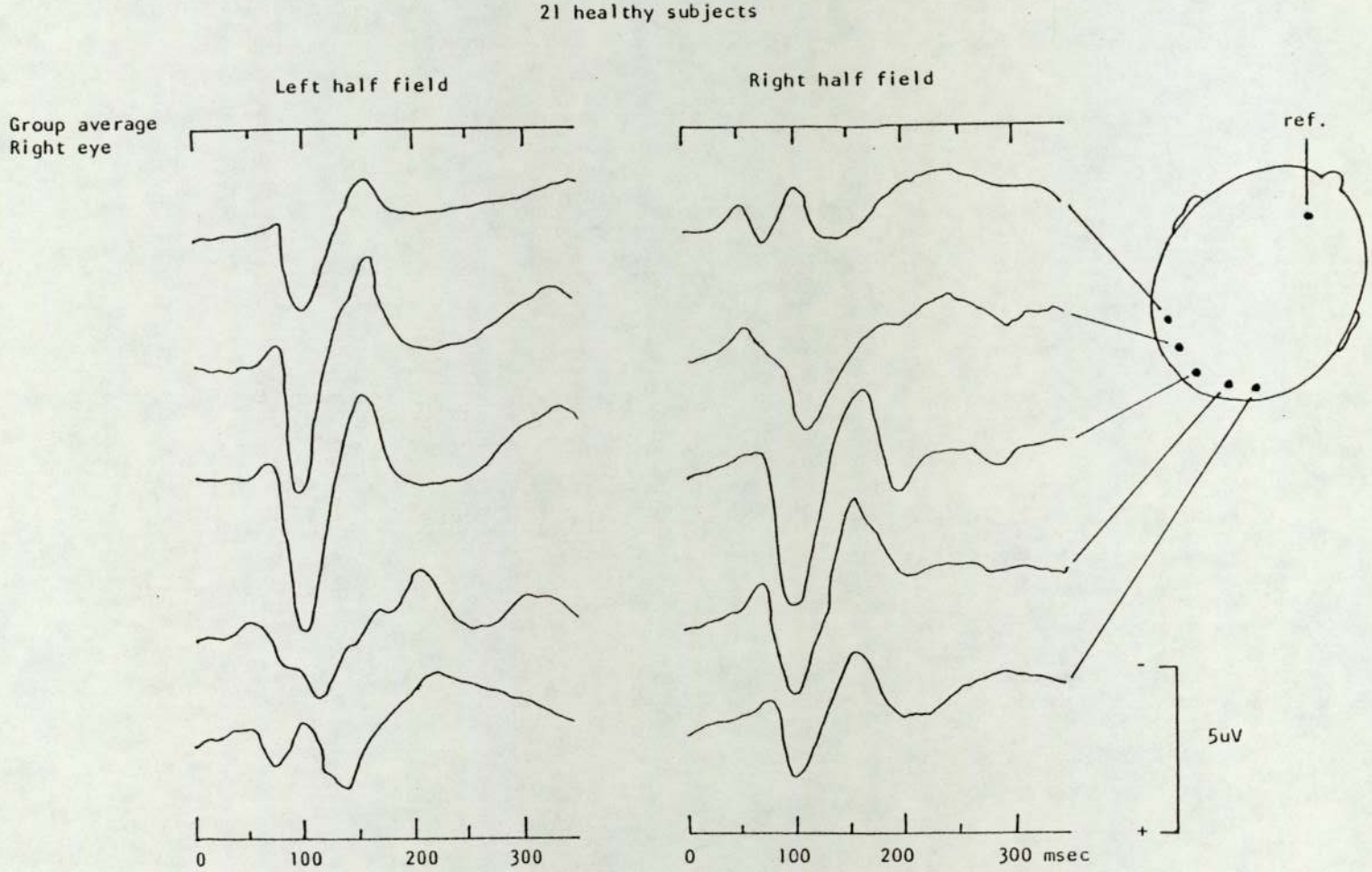


Figure 2.3 Group average responses to left and right half-field pattern reversal stimulation of the right eye. The P100 component is replaced by a PNP complex on the contralateral side at the electrode 10cm lateral to the midline (check size 50'; half field 0-16° radius)

(After Kriss et al. 1982)

For full field stimulation (16^{o} radius) in the patients before treatment, the grand average responses showed a broad positivity in the midline, peaking at 130ms (instead of 100ms) and to either side of the midline, there was a PNP complex. No significant inter-ocular difference was observed. A P100 ($\bar{x}$ = 111 ms) component was identifiable in 15% of the records of individual eyes accompanied by reduced amplitude. On a repeat investigation (the inter-investigation interval was not given), the P100 ($\bar{x}$ = 100ms) component was seen in 38% of the 13 returning patients with the amplitudes still significantly decreased; PNP complexes were seen in the remainder of the records.

With half field stimulation prior to treatment (refer to the normal findings given above), 64% of the records showed an ipsilateral P100 component whilst in the remainder, only the contralateral PNP complex was identifiable which spread over the midline in an attenuated form - the follow up trial did not produce marked changes.

Central field stimulation (4^{o} radius) prior to treatment, revealed VERs with P100 components in 39% of the records with reduced amplitudes; 36% of the records showed only PNP complexes and 25% had no discernible response. No improvement was seen after treatment.

Flash stimulation produced a broad positivity around 100ms incorporating several subpeaks in normals but 80% of the 15 patients showed a bifid (PNP) waveform which persisted on re-testing; however 18% of the controls gave this response. In 63% of the records, PNP complexes were seen for both flash and pattern stimulation.

These workers could not clearly understand how the PNP waveform seen in the flash response is associated with the presence of scotomata.

Once more these workers attributed the PNP complex seen to pattern stimulation as being a response to paramacular stimulation which agreed well with the extent of the scotomata. Their findings indicated to them that toxic optic neuropathy involves the papillomacular bundle with only partial recovery. This was also supported by the visual field study of Wilson and Reid (1969) and the contrast sensitivity study of Foulds (1981).

All ERG responses were normal unlike those reported by Krill (1970) and Ikeda et al (1978), however Kriss et al felt that it could be due to the different types of stimulation. In their analysis of the data, these workers did not include the variability of the results in the normals or patients. Nevertheless, this does not lessen the validity of their findings although it would help to observe how many patients fell outside the normal range.

Ikeda et al (1978) examined the ERGs and VERs of 83 patients with suspected optic nerve lesions. They observed the variation in the amplitude of the B wave of the ERG as a function of relative log intensity of stimulating flash, as well as the amplitude of the wavelets of the flicker ERG. The VERs were recorded from the mid-occipital electrode to pattern reversal stimulation (44' - 15° radius field). In the group of patients with toxic amblyopias, subnormal ERG function was seen, especially in the cone-mediated function. The VERs had subnormal amplitudes but without a delayed peak of the major positive component (about 100 ms) and without inter-ocular

difference in peak time. This result of unaffected peak latencies would be unlike what Halliday and his colleagues (1976; 1982), Van Lith and Vijkvinkel-Bruinenga (1978) and Van Lith and Henkes (1979) reported in their investigations on toxic amblyopes.

From the above results and those obtained from patients with other types of optic nerve lesions (multiple sclerosis, ischaemic optic atrophy, etc.), Ikeda et al suggested that the nutritional deficiency or toxicity could have a major effect upon the enzymic and transport processes of the relay cells rather than affecting the myelin sheath of the optic nerve. The proposition that the myelin sheath remains unaffected, is contrary to the postmortem findings of Victor et al. (1960); Victor (1963) and Victor and Dreyfus (1965) whereby they reported demyelination of the optic nerve.

Van Lith and Vijkvinkel-Bruinenga (1978) investigated the ERGs, the flash and pattern reversal VERs of 22 habitual and heavy drinkers with visual complaints (of which 16 were heavy smokers, 3 were moderate smokers and the smoking habits of the other 3 were unknown). In 7 patients (31.8%), the ERGs revealed abnormal or absent OPs, the B wave was more disturbed than the A wave and the photopic system more than the scotopic system. The amplitudes of the VERs to pattern stimulation were plotted against VA when it was found that 7 patients had normal values, 11 had very low responses whilst 3 had borderline responses; this result is presumably for the two parameters. Although it is mentioned that there is some relation between the amplitude of the responses and VA, no correlation factor has been given.

These workers also went on to observe the amplitude and latency of pattern reversal VERs after a fast intake of 35% alcohol in 3 patients. Recording was performed before and at periodic intervals up to 90 minutes after the intake of alcohol. They observed that the amplitude decreased and the latency of the most consistent component increased with time. The data from the chronic and acute studies implied that there could be both a direct and indirect toxic effect of alcohol which affects the retinal and conductive systems. Similar conclusions were reached in another study performed by Van Lith and Henkes (1979). These workers also felt that although vitamins A and B deficiencies may be present and in which case they should be given to the patient, there is no guarantee that a visual improvement will occur if the patient continues to drink as the condition is partly due to a toxic effect in the retina and visual pathways.

One of the relatively few groups of workers to present results on both electrophysiological and psychophysical tests is Leighton et al. (1979). They recorded light and dark adapted ERGs, VA, colour discrimination with the FM 100 hue test and central visual fields (this was not presented) on 7 recently diagnosed tobacco amblyopes who smoked 2-4 oz. strong pipe tobacco per week with 3 of them also smoking 10-20 cigarettes per day. 4 of them drank between 5-20 pints of beer per week, 2 were occasional drinkers and 1 was a teetotaller. The above tests were repeated after three months of treatment with hydroxocobalamin. There was an improvement in the VA, a significant reduction in the error score on the FM100 hue test and a marked increase in the light adapted B wave amplitude of the ERG. The change in the B wave amplitude was attributed to an

improvement in an abnormal biochemical state of the bipolar and possibly the Muller cells in the inner nuclear layer. This layer was postulated to be the site of the biochemical lesion and not the retinal nerve fibre layer or the optic nerve. These workers felt that these results were in agreement with those of decreased red foveal sensitivity obtained in a previous experiment (Bhargava and Phillips, 1974). Nevertheless, it is difficult to understand how these workers could preclude the possibility of damage to the deeper retinal layer and optic nerve when only ERGs were done.

In an investigation on optic nerve function in the toxic amblyopias and related conditions (for example, retrobulbar neuritis), Foulds (1981) claimed that the latency of the VER is a better guide than contrast sensitivity measurements to sub-clinical damage in apparently unaffected eyes. Although this statement was made, no data on VERs was given. Nevertheless, he reported that in the untreated condition of tobacco amblyopia, the contrast thresholds are high for all spatial grating frequencies, but recovery is accompanied by a reduction in the thresholds for low spatial frequencies. When VA has completely recovered, the contrast threshold for high frequencies often remains elevated and this with the common residual colour defect indicates that not all damage is reversible.

Hennekes (1982) found that the ERGs of 8 tobacco-alcohol amblyopes recorded under normal clinical conditions did not demonstrate any significant abnormalities in the A and B wave amplitudes. However, a significant reduction was seen in the maximum 'B' wave amplitude obtained with increasing light intensity and dark adapted conditions

indicating that this is a more sensitive method for detecting retinal disturbances. Nevertheless, all of the patients were already severely affected (VA $\leq$ 0.2). In addition to the studies performed on affected tobacco-alcohol amblyopes, there are many investigations which have been devoted to the effects of smoking and the acute and chronic effects of alcohol upon the ERGs and VERs.

Junemann and Dumaske (1968) reported changes in the ERG and contraction of retinal arteries after smoking one or two cigarettes in both smokers and non-smokers. These authors concluded that the retinal arteries of smokers are chronically narrowed.

The findings of various workers on the effects of smoking upon the flash VERs have been contradictory. Vazquez and Toman (1967) observed the flash VERs at a low intensity in 3 chronic smokers, 1) during chronic smoking, 2) during abstinence and 3) after the first cigarette following 36 hours of abstinence. During chronic smoking and following the first cigarette after abstinence, the negative 140ms and positive 160ms waves decreased in amplitude compared with the abstinence reading. No changes were seen in the earlier waves. These results were not in agreement with an increased arousal after smoking. However, the results were not sufficient for statistical analysis.

Hall et al. (1973) obtained different results with habitual smokers who abstained for 12 hours and 36 hours. At the lower flash intensities only, 8 out of 9 subjects exhibited significantly reduced amplitudes of the postive IV and negative V configuration (between 75 to 165 ms) during abstinence. The amplitudes returned to pre-abstinence values

after smoking the first cigarette. This was explained on the basis that smoking (allegedly nicotine) enhances the perception of weak stimuli.

Friedman et al. (1974) and Friedman and Meares (1980) recorded flash VERs 1) before and after cigarette smoking and 2) after 12 hours of abstinence. They found that the amplitudes of the later components (90 - 300ms) decreased during abstinence and increased after smoking, which is consistent with the arousal effect of smoking.

The discrepancy between the results could be partially due to the different electrode positions used by various workers. For instance, Vazquez and Toman (1967) recorded from the occipital area with a frontal electrode as reference as whereas Friedman et al. (1974, 1980), recorded from the mastoid with the vertex as reference.

Some workers also observed the acute effects of carbon monoxide (CO) on the VERs. Hosko (1970) and Stewart et al. (1973) investigated the effect of several levels of CO for exposure periods (10 min. to 24 hr.) in smokers and non-smokers. Not until the carboxylhaemoglobin levels (HbCO) exceeded 16-20% were any significant changes observed in the amplitude of the 2-3-4 complex and the latency of wave IV (N100).

Luria and MacKay (1979) performed two sets of studies on cigarette smokers and non-smokers. The group of tests employed, included scotopic sensitivity, reaction time, eye movements, optometric refraction for near vision, a perimetric test to white and red stimuli, an electroencephalogram and flash and flashed-on pattern VERs (38') which were measured

during a 3 hour period to air and a low level of CO. In the smokers, the mean scotopic sensitivity was markedly worse and the reaction times tended to be poorer. No marked changes were seen in the remaining tests and there was no evidence of an increasing difference between smokers and non-smokers with age.

However, it was noted that the mean HbCO level in smokers increased by only 4% (from 8 to 12%) whilst in non-smokers it increased by 7% (from < 2 to 9%). This suggested that either smokers handle CO differently to non-smokers or that smokers start at a higher level and approach saturation more quickly. Since the absorption curve predicted a linear function (that is there was an increase rather than a gradual deceleration in the HbCO level with prolonged exposure) it seemed to these workers that smokers absorb CO into their system in a different manner to non-smokers.

The studies which have examined the effects of the acute and chronic administration of alcohol will now be described.

Ikeda (1963) compared the ERGs of 3 subjects prior to and after the administration of ethyl alcohol (0.75 g/kg). After dark adaptation the ERGs evoked by a single flash at different light intensities as well as the flicker ERGs were observed. In the single flash study, there was no marked change in the latency of the B wave but the rise and recovery times and the amplitude of the B wave were increased; the A wave was not affected. In the flicker ERG study, the fusion frequency was lowered and the amplitude of the B wave was reduced.

These results indicated that a less intense stimulus is needed for a given amplitude of the B wave, that is, the retina becomes more sensitive to light but its response is substantially slowed so that it cannot follow a rapidly repetitive stimulus such as high frequency flicker.Since only the B wave was affected, the authors suggested that there was a change in the neural organisation which seemed to be an increase in the summative mechanism of the receptor neurones at the bipolar cells.

In 1970, Lewis et al administered a placebo of water and two doses of alcohol (0.4 g/kg and 1.23 g/kg) to 9 adults. The VEPs to flash stimulation were recorded at central and occipital electrode positions (electrode montage unclear) 30-40 minutes after the onset of drinking. No marked changes were seen in the occipital VERs with either dose. However at the central electrodes at the higher dose, there was an attenuation of some of the later components (later than 80ms), and the hemispheric asymmetry which was seen in some subjects prior to alcohol intake, disappeared after its administration. They attributed the attenuation of only the later components to the different sites of origin of the early and late components.

Cinotti et al (1970) examined 10 chronic alcoholics with liver disease. Peripheral and central visual fields, VA, colour vision (Ishihara test), dark adaptation and electroretinography were all performed on these patients. The first three tests did not reveal any significant abnormalities. The dark adaptation curve showed a delayed alpha point but the end point was within the normal range. The ERGs which were recorded in 1) a light adapted state and 2) at 1 minute and

10 minutes after dark adaptation, showed that the amplitude of the B wave in the dark was lower than the normal mean, however, it was not significantly different in the light adapted state. The recordings taken after dark adaptation failed to show any OPs. It is not clear if these workers obtained OPs on their normal tracings in the light adapted state but if they did not, it could be because they used the same intensity stimulus for all the ERGs. In order to elicit OPs in the light adapted state with background light, a higher intensity stimulus is required. (Tassy, 1966).

Cinotti et al. thought that the delay in the alpha point might have been associated with an abnormal vitamin B levels, however all the alcoholics had normal vitamin A levels. Other possible causes were suggested such as a change in the oxygen tension in the blood or a change in capillary calibre or a difference in the conduction of impulses. The added absence of the OPs also indicated a circulatory disturbance.

The animal study of Levett and Morini (1978) will be mentioned because of its interesting findings and conclusions. These workers observed the changes in the ERGs of frogs after acute (5-40%) and chronic (0.2-0.3% alcohol given up to 2 months) administration of alcohol. Under both conditions there was an increase in the latency of the B wave, accompanied by a disappearance of the E wave (an OP subsequent to the B wave). The ERG was also generally depressed in the chronic condition. After complete withdrawal from chronic alcohol intake, there was a transient overshoot in amplitude in comparison to pre-alcohol amplitudes before it settled down to a steady value,

accompanied by the reappearance of the E wave after some days. It was attempted to maintain the frogs on properly balanced diets during this experiment.

Levett and Morini postulated that since the Muller cell membrane behaves as a potassium ion exchange membrane and is capable of oscillatory behaviour, then both the B and E waves can be assumed to originate from the same underlying mechanisms. In chronic alcoholism there is swelling of the Muller cell membrane which may result in a diminished penetration of K+ through the membrane and a reduction in the light adapted OP.

Levett and Jaegar (1980) found similar effects on the B + B^1 waves (an OP) of the ERG of frogs when given alcohol under acute and chronic conditions. Investigations on the human ERG after acute alcoholic ingestion showed a reduction in the B^1 wave. They also reported an increase in the latency of horizontal saccadic eye movements, a deterioration of pursuit movements, an increase in the latency and duration of the accommodative response and an alteration in the pupilliary responses. Their results indicate that neural impairment begins with a blood alcohol level between 0.04-0.06% in man.

Posthuma and Visser (1982) investigated the VERs of 20 healthy controls, 20 chronic alcoholics without signs of brain damage and 16 alcohol induced Korsakoff psychotic patients. The results obtained from flash and pattern reversal stimulation (1^{o} 20' - 33^{o} field) showed that the controls had the shortest latencies of the P3 (P100) component. In the 2 patient groups, the latencies were longer and more variable

than those of normals. The increased peak latencies were more easily detected by pattern stimulation and were generally later in the patients with psychosis. Using a criterion of 2.5 standard deviations from the normal mean, 9 patients with Korsakoff's psychosis and 3 chronic alcoholics were delayed beyond the normal range. It was postulated that the VER could give evidence for the diagnosis of alcohol-induced brain damage. Perhaps if a smaller check size was used, the test would have been more sensitive.

Zuzewicz (1981) applied 1g/kg of ethanol to 30 healthy patients and examined their flash VERs after 30 and 60 minutes. The overall results from occipital electrode positions, demonstrated a prolongation of the latency time of all components with elevating blood alcohol levels. The amplitudes of the late components (94.5-223 ms) showed an initial increase (after 30 min.) followed by a reduction (after 60 minutes) but not returning to the original values. According to this worker the inter-hemispheric asymmetry disappearance as observed by other workers (Lewis et al. 1970), was only poorly shown in this study. However, the other workers only found this behaviour over the central regions and this may reflect non-specific later components and effects.

2.1.4. The Aetiology of Tobacco-Alcohol Amblyopia

In spite of a reasonable quantity of literature being available on tobacco-alcohol amblyopia, there is still much controversy regarding its pathogenesis. There have been many studies which have tried to reveal the modes of development and the most effective treatment for this condition. With regard to the mode of development, several

workers have postulated that there is an underlying nutritional defect which hinders the detoxification of substances contained in tobacco.

Schepens (1946) stated that tobacco amblyopia occurs when the intake of toxic substances (he suggested nicotine) exceeded the capacity of the liver to neutralise the poisons. During the war, he found that this liver deficiency occurred in chronically undernourished individuals who were only moderate smokers of a young age group. He did not find any therapeutic action from vitamins A, B_1 or B_2 and he felt that alcohol had little influence on the course of tobacco amblyopia.

Heaton et al. (1958) and Heaton (1962) cast some doubt on nicotine being a contributory factor in the development of tobacco amblyopia as large doses were given to laboratory animals and no optic atrophy ensued and histological damage in the CNS was rare. Heaton (1962) felt that CO was unlikely to be the cause because cigar smoke contains about twice the amount of CO in comparison to pipe and cigarette smokers yet tobacco amblyopia is rare in cigar smokers; also the histological features of CO poisoning were unlike those of tobacco amblyopia. He also felt that the amount or kind of tobacco and duration of smoking made little difference to the development of the disease. More recently, it has been reported that the level of CO is highest in cigarette smoke, however, this still does not dispute Heaton's argument (Smoking and Health Now, 1971). Harrington (1971) claimed that tobacco amblyopia occurs most commonly in elderly pipe and cigar smokers and rarely in cigarette smokers. From these two reports pipe smoking is the common factor.

Heaton and his colleagues (1958 and 1962) postulated that cyanide was the contributing element in tobacco amblyopia. He reported that with chronic cyanide poisoning in animals, peculiar brain lesions appeared with demyelination occurring more extensively than destruction of the axis cylinders. This he linked to the histology in tobacco amblyopia whereby optic atrophy, degeneration of the ganglion cells with glial proliferation and minimal interstitial proliferative changes take place.

However, Foulds et al (1974) pointed out that the amount of cyanide required to cause demyelination of the optic nerves in animals was so great that the animals became acutely ill and this was the reason why these workers thought that cyanide could not have a direct toxic effect on the optic nerve. Nevertheless, Heaton et al were not suggesting a direct toxic effect upon the optic nerve but that the cyanide was not being detoxified by hydroxocobalamin (vitamin B_{12}) to thiocyanate. In normal smokers, he found an increase in the amount of thiocyanate excreted which was compatible with the amount of cyanide in tobacco smoke whilst in tobacco amblyopes, he found lowered serum vitamin B_{12} levels in comparison to the normal smokers. He insisted that the hydroxocobalamin form of vitamin B_{12} was more efficient than the cyanocobalamin form for the improvement of visual symptoms. Many other workers supported the view that hydroxocobalamin should preferably be used (Chisholm, et al. 1967; Foulds, et al. 1968, 1969; Chisholm and Pettigrew, 1970; Chisholm, et al. 1970; Pettigrew, 1971; Satapathy and Reddy, 1981). It was even suggested that the use of cyanocobalamin might be harmful (Phillips and Ainley, 1968; Watson-Williams, et al. 1969; Foulds et al. 1971).

Foulds et al. (1968, 1969) like Heaton (1962), found significantly reduced mean serum vitamin B_{12} levels in tobacco amblyopes whilst the mean levels were similar in non-amblyopic smokers and non-smokers. They felt that tobacco amblyopia developed most readily in patients with insufficient dietary B_{12} or if the B_{12} absorption was defective; nevertheless it could still develop when tobacco smoking was moderate or in heavy smokers who had normal absorption and serum levels. They suggested that the hydroxocobalamin /tobacco ratio should be 3:5 in patients who continue to smoke (Foulds et al. 1970).

Wadia et al. (1972) investigated a large and undernourished vegetarian population (> 5 million) over a $2\frac{1}{2}$ year period and they postulated that if the effect of cyanide on serum B_{12} levels was a significant factor in the pathogenesis of optic nerve disorders, then a reasonable proportion of patients with tobacco alcohol amblyopia-like features should be referred to them.

Their results were on the contrary, in that only 20 cases were found which were all of sudden onset. Of these, 8 had the disease bilaterally (6 being smokers; 4 non-vegetarian cigarette smokers and 2 vegetarian cigarette smokers) and out of these 8, only 3 demonstrated centrocaecal scotomata (all 3 being non-vegetarians with substantial diets; 2 smoked and drank moderately). None of the patients had strikingly low serum B_{12} levels nor were their mean serum B_{12} and folate levels significantly lower than those of the control subjects. The plasma thiocyanate levels were definitely higher amongst smokers whether they were vegetarian or non-vegetarian in both patients and controls.

Of the 3 patients with bilateral centrocaecal scotomata one improved on corticotrophin whilst another began to improve before hydroxocobalamin was given. Amongst the other patients, they found that hydroxocobalamin, prednisolone and corticotrophin were all equally effective in producing visual improvement.

More recent work performed by Foulds et al. (1974), Bronte-Stewart et al. (1976) and Foulds (1981) had indicated various chemical pathways by which tobacco amblyopia could develop. They pointed out that although vitamin B_{12} plays a role in the detoxification of cyanide in tobacco or even beer or other cyanogenetic foodstuffs, it is by no means the only contributing substance. These authors as well as others (Heaton 1962; Wilson and Matthews, 1966; Wadia et al 1972) found that normal smokers excreted significantly increased amounts of sodium thiocyanate as compared with non-smokers; however, patients with tobacco amblyopia excreted reduced levels. They postulated that since sulphur is required in the detoxification process, then an inability to detoxify cyanide could be due to a lack of a suitable sulphur donor or from a breakdown in the conjugation of sulphur and cyanide. Evidence which suggests that there is an abnormality in the sulphur metabolism comes from the finding that tobacco amblyopes have a reduced erythrocyte level of glutathione (very rich in organic sulphur) as well as decreased concentrations of sulphur containing amino acids. Therefore, a dietary deficiency of protein might be an important factor in the development of tobacco amblyopia. Although an alternative route may be used when the cyanide to thiocyanate route is defective, it leads to the formation of carboxylic acid which inhibits the synthesis of myelin.

These investigators found that about 30% of their 100 patients had a poor diet, especially low in protein whilst somewhat under half were regular drinkers of spirits. Vitamin B_{12} deficiencies showed in 30% of the cases with a small minority having pernicious anaemia. Other workers had previously suggested that the retrobulbar neuritis seen in pernicious anaemia was due to the toxic effects of tobacco in the presence of vitamin B_6 deficiency (Freeman and Heaton, 1961; Smith 1961).

These authors concluded that vitamins B_6 and B_{12}, folic acid and sulphur containing amino acids, such as methionine and cystine are all important in the recovery of tobacco amblyopia as they form a part of the process from cyanide to thiocyanate.

They found that treatment with cystine rapidly normalises the biochemical picture and leads to recovery of vision even when smoking is continued. Phillips et al (1970) reported an improvement in 3 out of 4 patients with tobacco amblyopia who were treated with sodium thiosulphate and continued to smoke and drink.

Although the above workers believe that tobacco is the causative agent and alcohol is an inconsistent factor in the development of this gradual loss of vision, there are others who maintain that this condition can be caused by either 1) a combination of tobacco and alcohol or 2) by one of them. They have explained the genesis of this condition in a different manner, in that there is still an underlying nutritional factor but the detoxification of cyanide is not necessarily involved. These studies will now be mentioned. The suggestion of workers such as Harrington (1971), Reed and Drance (1972), that only alcohol

amblyopia reflects a nutritional defect and tobacco has a toxic effect on the optic nerve, seems to have been superseded by the current trends in thought about the aetiology of this condition.

Dreyfus (1965) examined the blood transketolase levels in 2 tobacco alcohol amblyopes and found that they were abnormally low, indicating a thiamine deficiency which he associated with a nutritional deficiency. Under normal circumstances, he found that the transketolase activity was the highest in the most medullated sections of the nervous system.

Victor et al. (1960) found that all of their 14 patients who were serious chronic alcoholics and heavy smokers showed general signs of malnutrition. The visual disorder was reversible to a large extent which seemed to the authors to be related with an improvement in the nutritional state of the patients in spite of continued drinking and smoking. These authors stated that the "amblyopia" which occurred under conditions of dietary restrictions such as that which occurred in the American prisoners of war in Japan and Korea in which alcohol and tobacco did not contribute, is clinically indistinguishable from the amblyopia seen in alcoholics. They thought that the aetiology of tobacco-alcohol amblyopia could not be due to a direct toxic effect on the visual pathways because the toxic amblyopia caused by say quinine, methanol tend to be abrupt in onset and often blindness is complete.

Saraux et al (1975) reported lowered zinc serum levels in 7 tobacco amblyopes whilst Sandberg et al. (1977) observed extremely low

vitamin A levels in 2 chronic alcoholics who had deficient diets. After the administration of vitamin A, there was a considerable improvement in the visual processes.

Dang (1981) stated that no single factor has been unequivocally shown to cause tobacco-alcohol amblyopia. He proposed a model for its development. Although he felt that cyanide from tobacco smoke played some role in its pathogenesis, he postulated that deficiencies in vitamins B_6 and B_{12}, folate, glutathione and sulphur-amino acids deplete the concentration of an essential chemical in the nervous system, called S-adenosyl-L-methionine, thus altering neurotransmission and myelination leading to the affection of the red-sensitive fibres initially.

Victor et al. (1960), Victor (1963) and Victor and Dreyfus (1965) performed post-mortem studies in a few individuals who suffered from tobacco-alcohol amblyopia and observed degeneration of the optic nerve fibres corresponding to the distribution of the papillo-macular bundle although not restricted to this area in all cases. In one individual whose retinae were examined, pathological changes were confined to the macular region where there was a profound loss of ganglion cells. In the retrobulbar portions of the optic nerve, the demyelination extended beyond the extent of the papillo-macular fibres but the type of gliosis seen in this region indicated that the lesions initially started in this area. This led these workers to believe that the pathological process possibly affected the optic nerve primarily with the retinal changes being secondary.

2.2 VISUAL DISTURBANCES CAUSED BY THE DRUGS USED IN THE TREATMENT OF TUBERCULOSIS

2.2.1 Development of Visual Studies on Ethambutol

a) Psychophysical Studies

Ethambutol* was first introduced in 1961 by Lederle Laboratories and is used as an oral agent against the tuberculosis bacillus, Mycobacterium tuberculosis. This drug is administered as a single daily dose and it is rapidly absorbed from the gastrointestinal tract with peak serum levels being reached after 2 - 4 hours (serum levels are proportional to the dose). 60-80% of a dose is excreted unchanged in the urine, 12% is excreted as metabolites and 8% is unabsorbed and excreted in the faeces (Place and Thomas, 1963; Place et al. 1966; Innes, personal communication). These figures demonstrate that efficient renal clearance is necessary and this has to be taken into account when deciding on the dose of Ethambutol to be prescribed.

Carr and Henkind (1962) were the first persons to report a deterioration in vision in 8 (44%) of their patients being treated with high doses of Ethambutol (60-100 mg/kg). It is interesting to note that 4 out of the 8 affected patients either suffered from diabetes and/or alcoholism which indicated that such cases are more susceptible to "Ethambutol" toxicity (also Meyer and Hoigne, 1980). Subsequent workers described disturbances in the visual pathways due to Ethambutol, sometimes used in conjunction with other drugs, such as Isoniazid (Place and Thomas, 1963; Leibold, 1966; Place et al. 1966; Mine, 1968; Yonekura et al. 1969;

* Ethambutol - 2,2' - (ethylene-diimino)-1-butanol-dihydrochloride.

Roussos and Tsolkas, 1970; Bouzas et al. 1971; Koliopoulos and Palmeris, 1972; Barron et al. 1974; Derka, 1975; Bronte-Stewart et al. 1976; Karmon et al. 1979; Foulds, 1981). Meyer and Hoigne (1980) listed the diminuition of VA and colour vision as the most important side effects of Ethambutol although they have been greatly reduced due to the lower dose levels currently used, consistent control of patients and simultaneous administration of vitamin B_6 (pyridoxine). However, it is not a routine procedure to give pyridoxine in every clinic.

The symptoms and signs which are characteristic of the ocular toxicity due to Ethambutol are as follows:-

1) A reduction in VA to 6/12 or less with the deterioration occurring quite rapidly once it has started; one eye is usually more affected.
2) A central or centrocaecal scotoma associated with a decrease in colour discrimination usually along the red/green axis. Constricted and central bitemporal field defects have also been reported (Figure 2.4, 2.5).
3) In many cases, the fundi appear normal, but optic neuritis, optic atrophy and hyperaemia of the discs have been observed.

In many cases of ocular toxicity caused by Ethambutol, there is a recovery or improvement in vision on cessation of the drug although deterioration in vision has been reported for a few months after abstinence (Mine, 1968; Yonekura et al. 1969; Bronte-Stewart et al. 1976).

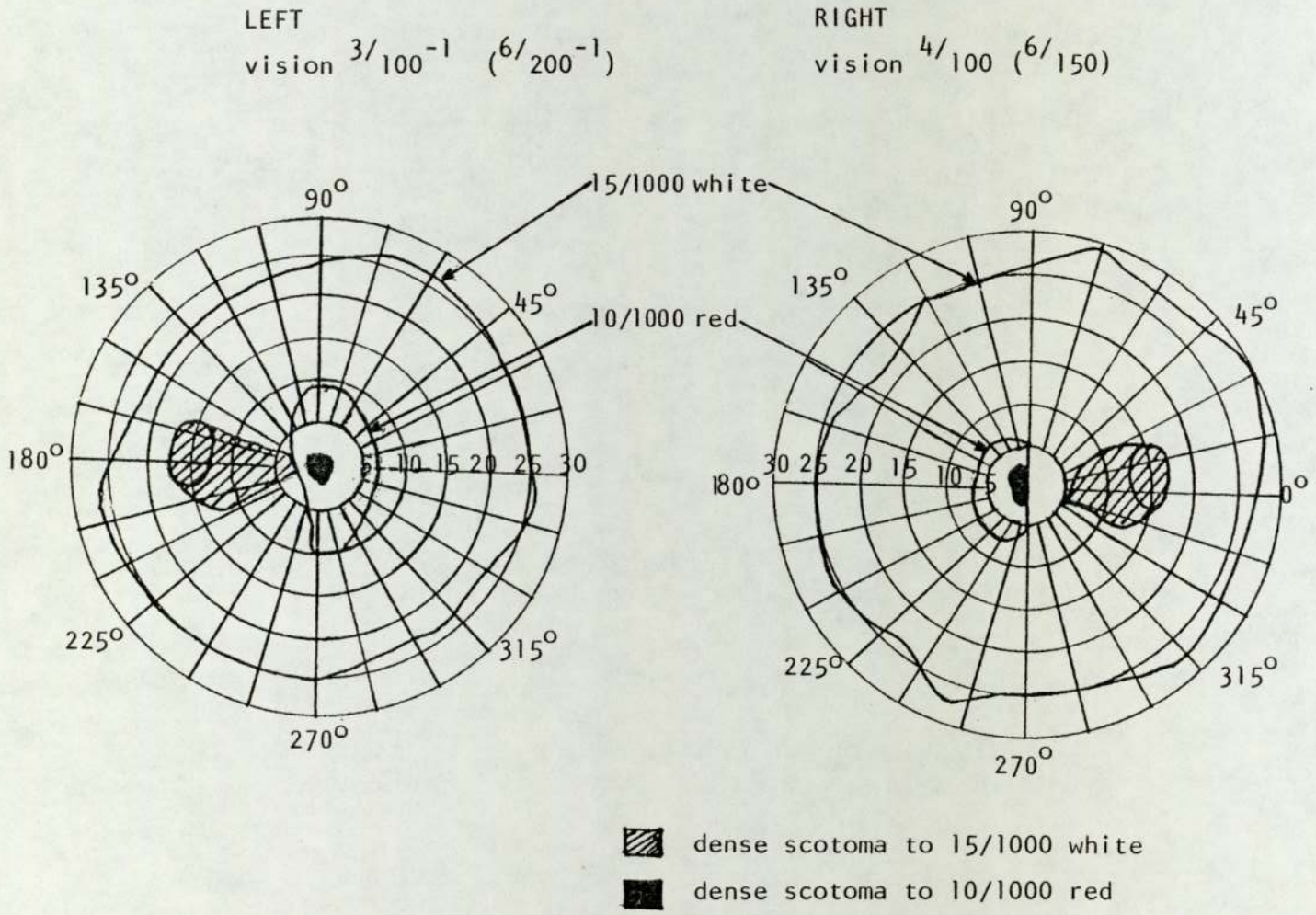
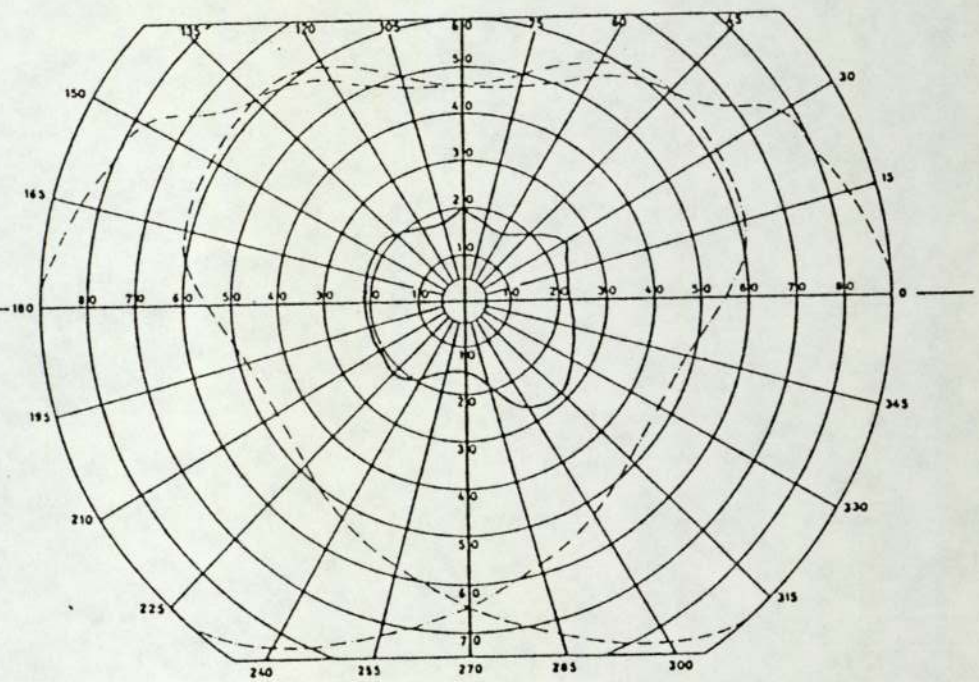


Figure 2.4

Diagram showing centrocaecal scotomata to relatively large white and red targets in a patient with Ethambutol toxicity, 12 days after reporting visual symptoms.

(After Carr and Henkind, 1962)

Left Vision $^{20}/_{20}$ ($^{6}/_{6}$)



Right Vision $^{20}/_{20}$ ($^{6}/_{6}$)

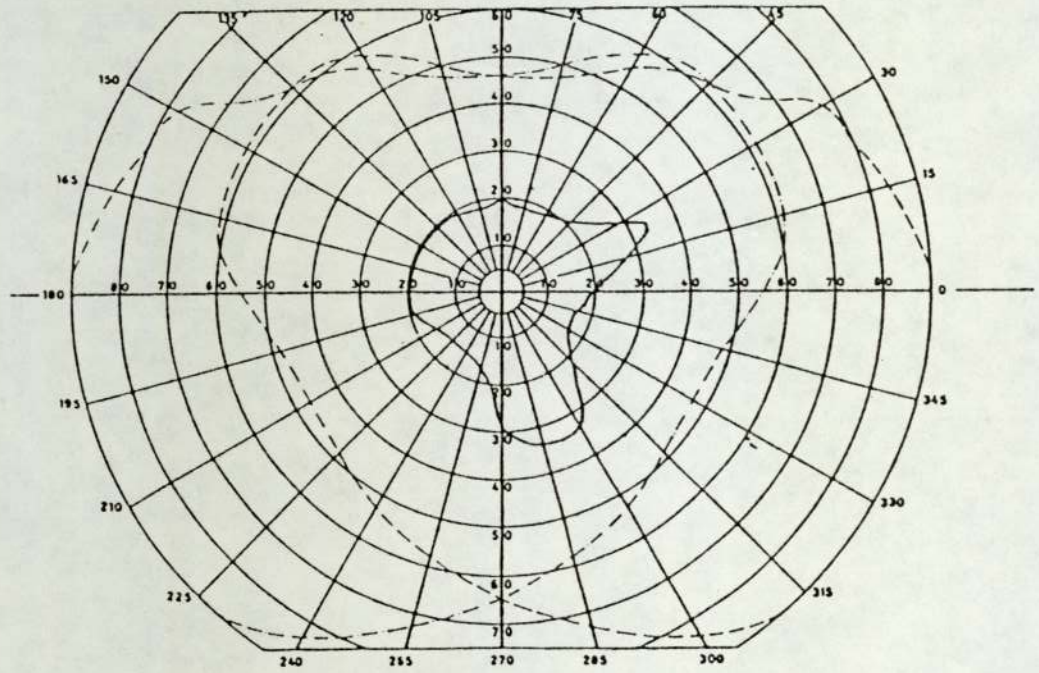


Figure 2.5

Diagram showing marked constrictions in the visual fields to $^{2}/_{1000}$W target, in a patient with Ethambutol toxicity, 6 days after reporting visual symptoms.

(After Barron et al. 1974)

The severity of damage which occurs in the visual pathways has been shown to depend on the dosage and to a lesser extent on the period of administration. Deterioration in vision has been reported as occurring from a few weeks to several months after the initial administration of Ethambutol (Bobrowitz and Gokulanathan, 1966; Donomae and Yamamoto, 1966; Leibold, 1966; Pyle, 1966; Place et al. 1966; Meyer and Hoigne, 1980).

Schmidt (1966) in his study on monkeys did not find any neurological symptoms and signs until a dose of 800 mg/kg/day was given for 6½ months. A lesion was found approximately in the centre of the optic chiasma, therefore causing disturbances to the nasal crossing fibres. With higher dosages more severe degeneration was found in the central areas of the optic chiasma, tract and nerve. Since a lesion was not observed until a very high dosage was administered, Schmidt suggested that the intoxication seen in humans employing lower dosages might only be irritative rather than destructive. However, in the study of Place et al. (1963) it was found that the 25 mg/kg oral dose curve (that is curve of average serum concentration versus time) for humans corresponded with a 50 mg/kg curve for monkeys, indicating that humans might be more sensitive to the drug. These authors reported a relatively high percentage (10%) of visual disorders amongst their patients but this could have been due to the comparatively large daily doses of 25-50 mg/kg. Meyer and Hoigne (1980) stated that they currently use a low dose of 10-15 mg/kg which may greatly contribute to the avoidance of ocular side effects. However, there are some cases of tuberculosis which cannot be controlled with such a low dose (Innes, personal communication).

Leibold (1966) divided his patients into two groups receiving greater than 35mg/kg and less than 30mg/kg respectively. He found that the incidence of developing an ocular toxicity as well as the degree of toxicity were increased in the higher dose group. For patients receiving therapy for at least 6½ months, 11 (31%) patients were affected in the higher dosage group in comparison to two (5.3%) patients in the lower dosage group. In the higher dosage group, 2 patients had not regained 20/40 or better VA after a 9 month follow-up and in the lower dosage group, 1 patient did not improve because of dense cataracts which were unrelated to Ethambutol.

Place et al. (1966) reported that 3 (42.9%) out of his7patients treated with 50mg/kg Ethambutol developed symptoms of abnormal vision during administration of the drug, which was continued for up to 4 months in the unaffected patients. Out of the 16 patients who were given 25mg/kg, 2 (12.5%) developed symptoms after 4 and 7 months respectively. The symptoms and signs of their patients were very similar to those already described, with no retinal changes observed. They also noted that there was no sex predisposition to the toxicity.

Mine (1968) observed an improvement in the ocular disturbances in 4 out of 6 affected patients after 3 months of cessation from Ethambutol. Four patients had shown normal fundi, 1 developed optic atrophy and the other had slight hyperaemia of the optic discs. The visual fields demonstrated enlarged blind spots in 2 cases accompanied by normal VAs, whilst the other 4 demonstrated central or centrocaecal scotomata with a concentric contraction of the field. Although the dosage is not mentioned, 3.3% of the total number of patients (180) was affected.

Roussos and Tsolkas (1970) observed 250 patients for one year who were being treated with Ethambutol and found that only 2% of their patients developed ocular defects on a dosage of 15 mg/kg. After 3 to 6 months of treatment, the toxicity of the drug was manifested in 3 cases in central defects and in 1 case, optic neuritis was seen as well. The fundus changes which were diverse, included haemorrhages, oedema and pigmentation of the macula. The VA of 1 of these subjects improved substantially after 40 days; there was not much improvement in another subject up to 3 months afterwards and the remaining 2 subjects never returned for subsequent examinations.

Friedmann (1970) recorded the visual fields of a female patient receiving 20 mg/kg Ethambutol who developed dense central defects in each eye. Although there was no improvement in VA after 3 months of treatment with hydroxocobalamin, the light thresholds on the Friedmann Visual Field Analyser demonstrated an improvement especially in the central field.

Bouzas et al. (1971) observed 180 patients between 2 to 9 months whilst under treatment with 15-20 mg/kg Ethambutol. 14 patients (7.8%) showed visual changes - 3 having papillitis and 11 having retrobulbar neuritis. 12 of these patients demonstrated less serious visual symptoms who were kept under surveillance whilst under treatment and eventually improved. The 2 patients who were affected most, were taken off treatment with satisfactory improvement occurring afterwards. These workers felt that all patients receiving Ethambutol should be kept under observation. According to Derka's data (1975), a rough estimate for the frequency of optic or retrobular neuritis is

0% for 20 mg/kg; 5% for 25 mg/kg and 10% for 30 mg/kg, however these figures seem to be on the low side.

Kolipoulos and Palimeris (1972) examined the colour vision of 180 patients receiving 15-25 mg/kg Ethambutol for 1 to 30 months with the Panel D-15 test, FM 100 hue test, Ishihara and AO HRR plates. 8 patients developed red/green colour defects 4 to 7 months afterwards, with 5 of them being mild without other ocular side effects; 3 patients showed yellow/blue defects of which 2 had diabetic retinopathy; 2 other elderly patients showed anarchic defects but this could have been due to ageing eyes or unsatisfactory co-operation.

Trusiewicz (1975) used the FM 100 hue test on 3 patients being treated with 25 mg/kg of Ethambutol and developing visual symptoms 5 - 18 months afterwards. 1 patient had only slight visual changes whilst the other 2 demonstrated substantial VA and scotomatous changes No ophthalmoscopic signs were seen. All 3 patients had defective colour discrimination being worse in the latter two. 2 of these patients were also receiving Rifampicin; in 1 of them, visual improvement occurred after Ethambutol was withdrawn and Rifampicin was continued whilst in the other patient, the 2 drugs were stopped simultaneously. However, Rifampicin has not been reported as causing visual disturbances. An observation which was made by this worker is that 1 patient developed -0.50 DS myopia in each eye temporarily.

The Medical Research Council (1973) presented a report in which one group of patients received 15 mg/kg Ethambutol, 0.75g Streptomycin and 300 mg Isoniazid and the other group, which acted as a control,

received Isoniazid, Streptomycin and p-aminosalicylic acid. In each case Streptomycin was discontinued after 3 months and the other 2 drugs were continued for about another 9 months. In the first group, 6 (6%) out of 99 patients developed visual abnormalities; 3 demonstrated central scotomata and another experienced blurred vision between 11 weeks and 8 months and only these 4 patients were taken off Ethambutol immediately. Improvement occurred in all cases although 1 patient continued to show a slight central scotoma until 12 months afterwards. In the second group, only 3 (3.4%) out of 89 patients suffered visual deterioration between 3 and 6 months, with 2 patients showing an improvement although the normal dose regimen was continued.

Surprisingly, Barron et al. (1974) only found 3 (1.03%) of their 304 patients affected with reduced VA and periaxial field defects being treated with 25 mg/kg for 60 days followed by 15 mg/kg of Ethambutol for an indefinite period.

Bronte-Stewart et al (1976) reported on 5 patients who experienced severe abrupt visual loss on the recommended dose regimen (as above). These patients also suffered acquired colour defects which were initially anarchic but during recovery (which was not always complete) often showed a red/green polarity. Vision tended to deteriorate for some months after cessation of Ethambutol, with recovery of vision being very slow, taking up to 2 years in 2 cases; in another case, the VA did not improve beyond 6/36. The visual field defects tended initially to be widespread, irregular, dense scotomata which showed a centrocaecal depression during recovery. Hyperaemia and swelling of the optic discs were replaced by primary optic atrophy. 3 of the 5 patients suffered from renal disease.

Bartholomew (1976) stated that early recognition of the visual deterioration caused by Ethambutol and cessation of the drug are important factors for full recovery as 4 of his patients developed toxic amblyopia over periods of 4 - 10 months whilst being treated with the recommended dosage (same as above dose regimen). On withdrawal of the drug, varying degrees of recovery occurred over 5-12 months.

Similar to Schmidt's findings, Asayama (1969) and Karmon et al (1979) reported central bitemporal hemianopias suggesting a chiasmal lesion. The latter workers reported it in an unsuccessful kidney transplant patient who was receiving Ethambutol (600 mg/day) and Isoniazid (200 mg/day). Visual abnormalities were noticed 10 months and 4 months after the onset of Isoniazid and Ethambutol respectively. Ethambutol was withdrawn 3 months before Isoniazid, with some improvement occurring one month after Isoniazid was stopped. This field defect could have been the result of the combined toxic effects of the two drugs as Isoniazid has been documented, to a lesser extent, as causing optic neuritis or optic atrophy (see Section 2.3.).

Nuding (1981) recommended that ophthalmological examination should be carried out before Ethambutol therapy and every 8 weeks during treatment. However, only 8 (0.5%) out of 6200 patients acquired symptoms of optic neuritis and required cessation of therapy. This low incidence of affection could have been partly because subjective visual problems did not influence the continuation of treatment. The dose levels were not given.

b) Electrophysiological Studies

Martino and Lamberti (1965) and Fillipone et al. (1968a and b) performed careful examinations in patients receiving 25 mg/kg Ethambutol for 4 to 12 months. They did not find any visual disturbances and there were no consistent abnormalities in the ERGs.

Tamai (1969) carried out scotopic and photopic (red stimulation) ERG examinations on 2 subjects being treated with Ethambutol, one had suffered severe visual disturbance with optic atrophy and the other only complained of transient diminuition in VA. After treatment had ceased for 7 months, the ERG of the first subject was subnormal in amplitude and revealed indistinct OPs although the latencies of the components were within normal limits. The ERG of the other subject was normal. No dosage was stated.

Meyer et al. (1974) recorded flicker ERGs at 2 Hz and 44Hz on 8 eyes with Ethambutol retinal toxicity. They also measured the minimum depth of modulation required to detect flicker at different frequencies of a 1^{o} test area surrounded by steady background light (De Lange curves see Figure 3.19). It was concluded that in both cases, high frequency responses were more attenuated than low frequency responses which they associated with a perifovealar lesion.

After 3 months, Babel et al. (1977) re-assessed the visual state of the eyes of 38 patients being treated with 1000 mg/day of Ethambutol, using scotopic and photopic ERGs and flash VERs. They found that during the first 3 months of treatment, 35.6% of the total number of eyes demonstrated abnormal ERGs especially in the photopic system

whereas 32.2% demonstrated abnormal VERs. After 3 months, when 10 eyes were re-tested, all of them showed abnormal ERGs and 75% revealed abnormal VERs. The aspects of the ERGs and VERs which were affected, were not mentioned and there is a discrepancy between the text and table which states 38 patients and 38 eyes respectively. Although the dosage per body weight was not given, an estimate of the dosage for average body weight would indicate that it ranged between 10mg/kg and 25mg/kg.

In 1979, Karmon et al. reported affected ERGs and VERs in a patient whose Ethambutol treatment ceased 6 days prior to testing. The conditions for testing were not given. This patient previously mentioned, was also receiving Isoniazid which was stopped after Ethambutol. Hennekes (1982) found that the ratio of the maximum B wave of the ERG under dark and light adapted conditions, was markedly reduced (with the dark adapted B wave being more affected) in 8 cases of severe Ethambutol toxicity receiving doses ranging from 750g over a 10 month period to 200g over 4 months.

Zrenner and Kruger (1981) performed psychophysical and electrophysiological tests on 2 patients who had taken 200g and 400g of Ethambutol respectively over an 8 month period. The first case had reduced VAs in both eyes and slightly pale optic discs. Her visual fields were concentrically narrowed, accompanied by a central scotoma and her colour defect was along the protan/deutan axes. She demonstrated a normal electro-oculogram and normal scotopic and photopic ERGs using coloured stimulation. However, the VERs revealed a latency delay to flash stimulation (that is, P100-125) and reduced amplitudes to pattern checkerboard stimulation (the method of pattern stimulation is not given)

of several check sizes with a 5^{o} field. With the foveal field blanked out and larger field sizes (up to 11^{o}), normal VERs were obtained for larger check sizes (up to 50'). The second patient also suffered reduced VA with a similar visual field defect and colour defect but to a worse degree. Once more, normal scotopic and photopic ERGs were obtained with the VER demonstrating an even longer delay to flash stimulation.

These workers then examined the spectral sensitivity functions of normal trichromats and of the two patients. They used either the psychophysical threshold or the VER amplitude criterion (that is, the amount of light energy required to give a VER of a pre-stated amplitude) to determine the spectral sensitivity to monochromatic lights between 400 and 650 nm, having adapted subjects to either coloured or white light. In order to obtain the curvesof the 3 cone functions on the receptor level (similar to Stiles's functions), these workers adapted the subjects to light which subdued the activity of other wavelengths except the region of the spectrum which they wanted to test. On the other hand, strong white adaptation was used in order to examine the action of colour opponent neurones (which are the only neurones which can shift the peaks to longer or shorter wavelengths). It was found that in both the normal and pathological subjects, all 3 receptor mechanisms (red, green and blue) could be demonstrated. However, with white adaptation, the curves of the pathological cases lacked one of the two dips in sensitivity, which is seen in normal cases. That is, the dip in the short wavelength region was present (490nm) but absent in the long wavelength (575nm), therefore making the curve single peaked in this region instead of double-peaked.

These results indicated to Zrenner and Kruger that in patients being treated with Ethambutol, the cells providing the antagonistic interactions between the red and green cone mechanisms were affected whilst the receptors and their individual pathways up to the visual cortex remained unaltered since the ERGs were normal and the 3 receptor mechanisms could be demonstrated with the VER amplitude-criterion method. However, other workers have found abnormal changes in the ERG (Tamai, 1969; Meyer et al 1974; Babel et al 1977; Karmon et al. 1979; Hennekes, 1982). Perhaps the discrepancy in the ERG results could be due to different dose levels.

The results of Zrenner and Kruger (1981) suggest that the red/green colour opponent cells have been damaged which other workers have found to be predominantly of the sustained type (Gouras, 1972; DeMonasterio et al. 1975; DeMonasterio, 1978). However, the high frequency attenuation of flicker found by Meyer et al (1974) would indicate that the transient cells are mostly affected from the observations that transient (phasic) cells are best activated by high temporal frequencies whilst sustained (tonic) cells respond maximally to low temporal frequencies, (Movshon et al 1978; Gouras, 1980). It might be that both types of cells are affected but then relative affections are noted at different stages of the disease.

2.2.2. Aetiology of the Mode of Action of Ethambutol and Isoniazid on the Visual Pathways

Buyske et al. (1966) reported that the chronic administration of relatively high doses of Ethambutol to laboratory animals could cause a

loss of zinc and copper in selected tissues, including the eye. With this evidence, Place et al. (1966) decided to observe serum levels of these two metals in their investigations on humans receiving Ethambutol therapy. They found that there was no change in the serum levels of copper but there was a moderate decrease of zinc serum levels and an increase of zinc in the urine of 2 patients studied. Saraux, et al. (1975) also confirmed this finding of reduced levels of zinc in the serum during Ethambutol therapy.

It has been postulated that the high concentration of zinc found in the retina and optic nerve may be necessary for normal nerve function through its role in axoplasmic transport (that is, it supplies materials to the axonal synaptic terminals and subserves growth and maintenance of the axon (Edstrom and Matisson, 1975). Yolton (1981) suggested that in humans, chelation of zinc by Ethambutol or Isoniazid (that is, Ethambutol and Isoniazid are able to fix zinc into their molecular structure) could make the zinc unavailable for axoplasmic transport, resulting in the symptoms of optic or retrobulbar neuritis.

2.2.3. Development of Visual Studies on Isoniazid

Isoniazid*, like Ethambutol is a chemotherapeutic agent in tuberculosis therapy which first attained prominence in the literature in 1952. It is given as a single oral dose and attains its maximum serum level after 1½ to 2 hours after administration. Similar to Ethambutol,

* Isonicotinic acid hydrazide

efficient kidney function is necessary as 75-95% of a dose of Isoniazid is excreted in the urine within 24 hours (Kratka , 1954; Meyer and Hoigne 1980).

The main side effects of this drug involve the peripheral and central nervous systems. Polyneuritis occurs most frequently after the third week of treatment with symptoms of sensation of burning feet, of heat, cold and strain particularly in the muscles. The population of patients who take Isoniazid can be divided into two genetically different groups as regards their metabolism of the drug, that is the slow and rapid inactivators. This depends on the rate of acetylation of the drug by the liver. However, this difference in the metabolism of Isoniazid does not present a significant problem as the doses used today do not usually permit the drug to reach unacceptably high serum levels. Nevertheless, the slow inactivators are said to be more likely to develop peripheral polyneuritis as Isoniazid (especially in high serum levels) binds with a pyridoxine-based enzyme (pyridoxal-5-phosphate) making this enzyme unavailable for certain metabolic processes. The resulting compound is excreted in the urine. As a result of this, a deficiency of pyridoxine ensues and leads to polyneuritis (Meyer and Hoigne, 1980). However, pyridoxine is still not simultaneously given with Isoniazid in all clinics.

The side effects seem to be dose-related, however, with the present dose levels of 4-6 mg/kg/day, peripheral polyneuritis only occurs in about 1-2% of the patient population, with diabetes, alcoholics, epileptics and malnourished individuals being more susceptible (Kratka, 1954; Weinstein, 1975; Meyer and Hoigne, 1980). One of the secondary

toxic side effects of Isoniazid therapy is the occurrence of visual difficulties but the number of reports on this subject is not as numerous as for Ethambutol. The symptoms and signs of Isoniazid ocular toxicity are very similar to those for Ethambutol.

Sutton and Beattie (1955) and Keeping and Searle (1955) each presented a case history of a patient with ocular toxicity whilst on Isoniazid treatment for tuberculosis. The patient of the former workers was receiving 15g p-aminosalicyclic acid and 200 mg Isoniazid daily whilst the patient of the latter workers was getting 1g p-aminosalicyclic acid and 200 mg Isoniazid. Visual symptoms were experienced 10 and 25 days respectively after the initital intake of these drugs. As Isoniazid ocular toxicity had not been previously reported, Sutton and Beattie did not discontinue the drugs until after 6 weeks when visual difficulties persisted and bilateral optic atrophy developed. No other fundus changes were seen in the meantime. These authors concluded that the visual deterioration was due to Isoniazid as p-aminosalicyclic acid had previously been given to this patient and it was well tolerated. Fortunately, for the patient of Keeping and Searle, when the medication was stopped after 6 weeks, there was a return to normal vision within 1 month. Although it appears that Isoniazid was the cause of the visual disturbances, it seemed to have been enhanced by the simultaneous administration of p-aminosalicyclic acid as the patient with the lower dosage of this drug, recovered.

Janssen and Boke (1955) observed an increase in optic nerve lesions in patients with tuberculosis meningitis who were treated by injection of Isoniazid and Streptomycin as compared with those treated with Streptomycin ~~as above~~ alone.

Dixon et al. (1956) reported 5 cases of polyneuritis, out of which 2 developed visual symptoms. One of these patients was receiving a high dose of Isoniazid (18.5 mg/kg) as well as p-aminosalicyclic acid (15 g/dy) and Streptomycin(1g/day) when visual difficulties came about after 4 months. The right optic disc was slightly swollen although vision was not impaired. However, the left eye showed some consecutive optic atrophy and impairment of vision. The polyneuritis gradually improved with vitamin B concentrates. The other patient, who eventaully died, received 6 mg/kg Isoniazid and 1g Streptomycin twice weekly, and visual symptoms were experienced after 5 weeks, leading to bitemporal hemianopia and finally complete blindness after 5 months although the ~~other~~ optic nerve heads remained normal. Post-mortem studies demonstrated no obvious lesions in the optic nerves or chiasma. However, the optic tracts showed symmetrical softening and demyelination of the superior and median positions.

Kass et al. (1957) described visual disturbances in 2 patients. In one patient who had recurrent episodes of tuberculosis, the dosage was increased to 16 mg/kg accompanied by the administration of vitamins B_1 and B_6. In another patient, who was an alcoholic the dose was 9 mg/kg. The first patient developed visual symptoms and polyneuritis after 6 weeks. Both optic discs appeared red on the nasal side and showed some pallor on the temporal side with pigmentary changes. Her visual fields revealed concentric constriction with a great improvement in her visual fields and VA within 6 months. The alcoholic patient suffered ocular symptoms after 30 days which included retro-orbital pain and slight papilloedema, leading to blindness in both eyes. It should be remembered that alcohol and

general malnutrition could have contributed to this patients visual deterioration although no changes were seen until Isoniazid was administered. On the death of this patient, it seemed as if optic atrophy was developing.

Money (1959) reported 16 cases of polyneuropathy among tuberculous undernourished patients in Nigeria who were getting 4-6 mg/kg Isoniazid. He remarked that one of these patients had bilateral acute retrobulbar neuritis.

Kalinowski, Lloyd and Moyes (1961) observed that only one patient developed mild optic neuritis which did not progress to optic atrophy in a study of 3148 patients receiving various combinations of Isoniazid, p-aminosalicyclic acid and Streptomycin. Peripheral neuritis which was more common, was seen in only 0.3% of patients who received Isoniazid. These workers pointed out that there is a virtual lack of marked toxicity on a dosage of 2-5 mg/kg Isoniazid, however, it increased with larger doses especially in susceptible patients, for example, chronic alcoholics.

The investigation of the Medical Research Council (1973) and Karmon et al. (1979) which involved the administration of Isoniazid have already been mentioned.

The third drug, besides Ethambutol and Isoniazid which is to be used to treat the tuberculous patients taking part in this project is Rifampicin (which is an anti-tuberculous antibiotic). However, this drug has not been recorded as causing ocular side effects.

Its adverse reactions are usually gastrointestinal intolerance (appearing as nausea, stomach ache and lack of appetite) and liver disorders (Martindale, 1977; Meyer and Hoigne, 1980).

Before closing this section it should be said that in the treatment of tuberculosis, two or more drugs are simultaneously used to combat the tubercular bacteria. This method of treatment is more effective due to drug synergism and the combined ability of the drugs to destroy more resistant organisms (Kratka, 1955; Kalinowski et al. 1961; Meyer and Hoigne, 1980).

2.3 HISTORY AND DEVELOPMENT OF STUDIES INVESTIGATING "A BILATERAL FORM OF AMBLYOPIA" SEEN IN WEST INDIANS AND AFRICANS

With the advent of many West Indians to Britain chiefly in the mid-1950's and early 60's and to a lesser extent persons from Africa, a bilateral form of amblyopia has been found to occur in these people which has created interest amongst members of the medical profession (mainly ophthalmologists), (Behrman, 1962; Crews, 1963; MacKenzie and Phillips, 1968; Ikeda et al. 1978). This condition has often been referred to as "West Indian Amblyopia".

From 1888 and 1897, Strachan had reported from Jamaica on 510 cases with ataxic and polyneuritic disturbances, reduced vision with optic atrophy and deafness. Later, Scott (1918), Whitbourne (1947) and Carroll (1947) presented papers about a nutritional retrobulbar neuritis in sugar cane labourers and in children in Jamaica who demonstrated central scotomata and in many cases impaired colour

vision ~~in many cases~~, eventually leading to pallor of the optic disc. Unlike Scott, Whitbourne and Carroll found very few patients showing ataxic changes, however deafness seemed to have been fairly common. In the case of the latter workers, cod-liver oil, yeast, vitamin B preparation and improved diets were used as treatment, when visual ~~impairment~~ improvement was noticed in those children in whom early diagnosis had been made.

Degazon (1956) who concentrated on the ocular complications of this condition in Jamaica found that the majority of his 298 patients revealed central or paracentral scotomata (about 80%) and a lesser number had constricted peripheral fields (about 5%): however, they never progressed to blindness. He felt that malnutrition played little or no part in the development of this condition and if treatment (vitamin B preparations) was going to be successrul, there had to be a short onset of symptoms. Like Scott, Degazon suggested that toxic factors were involved in the case of central scotomata, and diminished blood supply in the case of constriction of the visual field.

Cruickshank et al. (1961) and Montgomery et al. (1964) described this neuropathic syndrome as developing quickly for some 6 months, then becoming stationary in most cases, although a slow deterioration can still occur in some individuals. They found spastic paraplegia and posterior column damage in some of their patients; however optic atrophy and deafness were mostly seen in the minority of patients (10%) who mainly had a sensory ataxia. The authors did not find that vitamin B preparations were very effective in treatment.

In addition to the West Indies, reports have also come from Africa of individuals suffering from neuropathic syndromes which all presented cases of retrobulbar neuritis and /or optic atrophy. Monekosso (1962) claimed that the spastic syndromes were common in Jamaica whilst in Nigeria the ataxic, non-spastic syndrome was more common. Stannus (1912) Wright (1928), Clark (1925), Moore (1937, 1946 and 1966) all described cases of pellagra in Africa. Yeast, cod-liver oil and Marmite were found to bring about an improvement in visual disturbances and Moore, like some of the other workers pointed out that early diagnosis was essential. Both Moore and Clark attributed the condition to the high dietary intake of cassava derivatives possibly causing toxic effects.

Money (1959), Monekosso and Wilson (1966), Osuntokun (1968), Osuntokun et al. (1968) found an ataxic neuropathy occurring in patients in Jamaica and Nigeria with a monotonous diet of cassava derivatives. The authors of the latter three papers described high plasma thiocynate levels in their patients which made them conclude that this represented detoxicated cyanide which is present in the cassava. Osuntokun (1968) reported a fall in plasma thiocynanate levels with an improved diet, containing little or no cassava. Osuntokun et al. (1968) found an absence or diminuition of sulphur containing amino acids which are required for the detoxification of cyanide to thiocyanate. This is very similar to the reports made about tobacco amblyopes (Foulds et al. 1974; Bronte-Stewart et al. 1976).

Osuntokun et al. (1969) conducted a survey of the neurological abnormalities occurring amongst the inhabitants of two villages in Nigeria, who were preselected because one village had a high cassava consumption

and the other had a low cassava consumption. It was seen that a degenerative neuropathy occurred at a significantly higher frequency in the village with high cassava intake and once more, the plasma thiocyanate levels were increased in this group. This again suggested that the larger concentration of cyanogenetic material in the outer integument of the tuberous root (especially the bitter Manihot/Utilissma eaten in Nigeria) penetrated inwards to contaminate the edible part which lead to this ataxic neuropathy. Treatment was carried out with hydroxocobalamin, riboflavin and cystine but no conclusive results were yet available.

The patients of West Indian and African origin who have presented themselves with bilateral amblyopia in the eye hospitals in Britian seem to have less severe neurological signs and symptoms than the patients reported from the West Indies and Africa.

Behrman (1962) examined 17 patients with bilateral amblyopia who failed to reveal any other abnormality in the general medical and neurological examinations performed. He found central scotomata in 12 cases and peripheral constrictions in 4 cases of varying degree accompanied by pallor of the discs in 11 patients and defective colour vision on the Ishihara plates in all cases. This investigator felt that the possible causative factors of this condition in the West Indies (which included alcohol, "bush teas", syphilis, bright sunlight etc.) could be eliminated in most of his patients especially those who showed symptoms some time after taking up residence in Britain. He suggested that it is an African race-influenced disorder of sporadic incidence as all of his patients were African or of African extract. This worker in conjunction

with Arden and Kelsey did not find abnormalities in the ERGs and EOGs of 2 West Indian patients.

Crews (1963) found central scotomata of varying shapes in 12 out of 22 patients, especially to red and green targets with 2 other patients demonstrating peripheral contractions. 18 patients had partial or total pallor of the optic discs whilst 3 other patients were doubtful cases. Only 1 case showed abnormal pigmentary changes of the maculae. The majority of the patients had VAs between 6/60 and 6/18, never progressing to blindness. This worker suggested an adequate diet with no intake of toxic substances as well as a course of yeast, vitamin B_2 complex with vitamin B_{12} could be tried in those patients suffering from recent visual loss. However, until the time of writing this paper, he had found no improvement in his patients on this course. This author indicated that the cyanide from cassava (also eaten in the West Indies) as well as bush teas could be influencing factors. However, there was no evidence that either geographical or class distribution, tobacco, alcohol or any special bush tea was the primary cause although he felt that most of the patients would have suffered periods of privation.

Owen (1966) also found central scotomata (especially to red) and pallor of the optic discs in 10 West Indian patients with no ~~ocular or~~ neurological signs. From Owen's observations and past evidence from studies carried out in the West Indies on children, he concluded that the condition is due to nutritional deficiency in childhood, since 1) it became static without improvement with vitamins, 2) 8 of the 10 patients affected, had poor eyesight for many years and 3) a similar condition occurred amongst prisoners of war which was due to malnutrition. Owen also

thought that there were other influencing factors, such as tobacco, alcohol, pernicious anaemia, bush teas.

MacKenzie and Phillips (1968) examined 10 West Indian patients with no other neurological signs and found scotomatous field defects which were scattered and variable in shape and density, often connected with the blind spot and /or break through to the periphery. They stated that the lesion was likely to be subchiasmal as there was no homonymous or bitemporal pattern in the visual fields. Although they thought that there was a slight resemblance to the field defects in tobacco amblyopia, they did not feel that tobacco was the causative agent (as only a minority of their patients smoked) but perhaps cyanide poisoning could be a common factor.

In 1 subject suffering from "West Indian Amblyopia", Ikeda et al. (1978) found that the amplitudes of the ERGs (particularly in the cone mediated ERG) and pattern reversal VERs were markedly reduced although the delay in peak latencies was not significantly different from normals. Similar to tobacco amblyopia, these workers felt that these results suggested a nutritional or toxic malfunction which could affect the enzyme and transport processes of the relay cells and axons rather than the myelin sheath of the optic nerve.

The results of Ikeda et al (1978) to pattern reversal stimulation are in disagreement to those of Harding et al. (1978) whereby they reported patients with West Indian amblyopia (with central scotomata) showed a triphasic response (PNP response) similar to the type of response which Halliday (1976) obtained in toxic amblyopia.

From the writings of Behrman, Crews, MacKenzie and Phillips, it appears that this condition yields visual field defects of variable shapes and densities, very often in the central area, sometimes breaking through the periphery or in some instances, they are confined to peripheral constrictions. The age of onset extends over a wide range but "the degree of amblyopia" seems to become stationary after a certain time, not leading to blindness. Behrman (1962) indicated that there is an active phase of rapid development, after which time there is no further deterioration.

The electrophysiological results are contradictory with certain workers reporting normal ERGs and EOGs (Behrman et al. 1962) whereas others found reduced-amplitude ERGs and pattern VERs (Ikeda et al. 1978) and increased latencies of the pattern and flash VERs (Harding et al. 1978).

From the above evidence, it can be seen that the aetiology of this condition which presents itself in West Indians in Britain still remains obscure. The investigators who have studied this disease have indicated that it is related to a dietary deficiency which seems to involve many influencing factors. However no one substance or group of substances have been identified as being the primary cause. This uncertainty has been further complicated by the fact that accurate case histories were difficult to obtain in spite of exhaustive efforts.

Behrman (1962) suggested a race-related influence but on the other hand Owen (1966) felt that this condition resembled the condition which occurred amongst American prisoners of war in Korea and Japan which would indicate that it is not confined to individuals of African origin.

As a result of this uncertainty of the substances which give rise to this condition, a control patient group has not be included.

2.4. SUMMARY

From the above descriptions of the proposed aetiologies of the conditions to be investigated in this project, one common feature becomes evident, that is an underlying nutritional factor has been indicated in each case. However, the modes of development and the treatment of the conditions are not necessarily similar.

On considering tobacco-alcohol amblyopia, the studies have produced results revealing affections of colour discrimination, visual fields and contrast and flicker sensitivity and in the case of ERGs and VERs, they have been shown to be effective in detecting changes at the retinal and retrobulbar levels. It has even been claimed that VERs are more useful than certain psychophysical tests (contrast sensitivity, VA), in detecting subclinical damage in demyelinating diseases (Halliday, 1976; Reimslag et al. 1981; Foulds, 1981). Nevertheless, most of the studies have been devoted to investigating one or two aspects of the condition (for example, changes in the ERGs or colour discrimination) and although each study is valid in itself, it becomes difficult to assess their comparative usefulness as an aid to diagnosis since the experimental conditions vary in each instance, thus altering the criteria of normality.

The dose levels of Ethambutol which are currently prescribed vary between 15mg/kg to 25 mg/kg and in the case of Isoniazid, it is 4-6 mg/kg .

Even at 15mg/kg, it has been reported that about 2% of the patients suffer from visual defects, increasing to about 10% at 25mg/kg. (Place et al. 1966; Roussos and Tsolkas, 1970; Bouzas et al. 1975; Meyer and Hoigne, 1980). Unfortunately those who are affected experience a reasonably rapid deterioration in vision which can take up to 2 years to recover (Foulds, 1981). The investigations which have been performed on Ethambutol and Isoniazid toxicities have been mostly psychophysical. The relatively few electrophysiological studies which appear in the literature have generally been done on small numbers of patients who are usually so badly affected that there are very definite changes in the results of the VERs and ERGs. In this project, a group of visually symptomless patients are to be examined before and after treatment for tuberculosis to see if any early changes can be detected before this deterioration in vision occurs. Although Babel et al. (1977) repeated patients who were on Ethambutol treatment, the patients were not tested prior to treatment to obtain control data; the components of the VERs and ERGs which were affected, were not mentioned and the dosages per body weight were not stated.

The primary cause of West Indian amblyopia still remains a mystery although many possibilities have been suggested. It is hoped that by studying these patients some particular trend might be seen in the data which could lead to earlier detection. It has been indicated that if treatment is going to be helpful at all, it should be started fairly soon after the onset (Crews, 1963). From the publications produced in this country it seems as if treatment has proved disappointing. Maybe, this is because the patients have presented themselves too long after onset.

Like Ethambutol and Isoniazid toxicity, most of the studies carried out on West Indian amblyopes have been psychophysical, with contradictory findings in the electrophysiological studies. If any additional information can be obtained from the variety of tests used in this project it is possible that there could be an early indication of any visual changes taking place, when treatment could be started and the patients diet considered in more detail. In the investigations, a dietary privation is suggested and Crews (1963) pointed out that by migrating to a different country the dietary habits do not necessarily change.

In conclusion the aim of this project is to examine the visual mechanisms of two patient groups for each condition (except for West Indian amblyopia for reasons already explained), that is one group which is actually affected and another group which has not presented with any visual symptoms but is receiving the causative substance on a chronic basis. Very few studies have simultaneously examined patient groups of this type and none of them have employed the cross-section of psychophysical and electrophysiological tests to be used in this project. As can be seen from the preceding sections most investigators have focussed their attention to either psychophysical or electrophysiological methods, therefore an estimation of their relative usefulness cannot be easily made. In the estimation of visual fields which is an important aspect of testing, much of the work has been qualitative employing kinetic perimetry which is less satisfactory for follow-up assessments than static perimetry; in addition to this, kinetic perimetry suffers from a higher probability of variability in assessing the visual field (See Section 3.3). There has been a small number of electro-

physiological tests performed on persons suffering from Ethambutol toxicity and West Indian Amblyopia, quite often giving contradictory results.

In this study, some well established and useful clinical tests will be used in conjunction with relatively new research techniques (such as VER coloured pattern stimulation) which have been chosen because from past evidence about the affection of the visual system by the conditions, it is thought that they should provide some useful information and probably employed as effective diagnostic tools in detecting early visual changes.

CHAPTER 3

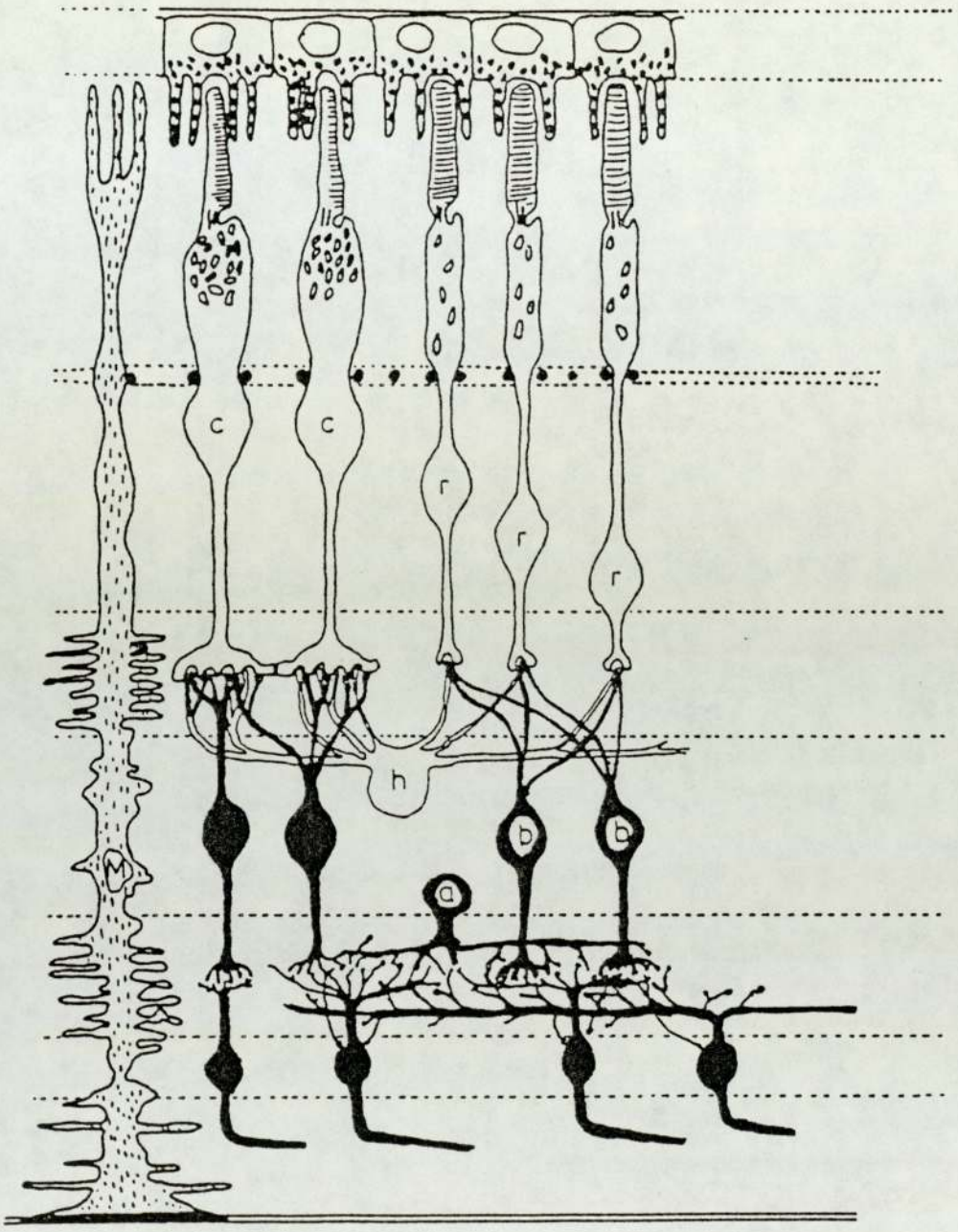
HISTORY AND DEVELOPMENT OF THE TESTS TO BE USED IN THIS PROJECT

HISTORY AND DEVELOPMENT OF THE TESTS TO BE USED IN THIS PROJECT

In this chapter, the development and function of the tests to be performed will be discussed in order to demonstrate their investigatory usefulness. The first topic to be presented is the electroretinogram, however a brief description of the nature and neural function of the retina will precede the account on the ERG, as it will be relevant to all of the following sections.

The retina is the light receptive region of the eye responsible for converting light energy into nervous impulses for transmission to the higher visual pathways. It is a complex layer of nervous tissue which is capable of receiving sensory responses of enormous variation in quality and quantity. It is similar to other nervous tissue in that it consists of nerve cells which synapse with each other to form a series of neurones. The retina itself consists of ten layers composed of pigment cells, photoreceptors, nerve cells (photoreceptor, horizontal, amacrine, bipolar and ganglion cells) and glial (Muller) cells (Figure 3.1). The neural information in the retina is not simply relayed from one layer to another, but there is also lateral interaction via the horizontal and amacrine cells.

The detailed physiology and histology of the retina are beyond the scope of this thesis and the reader is referred to Davson (1980). However, in order to understand the nature and neural function of the retina, the areal distribution of the rod and cone photoreceptors will be presented as well as the distribution of the ganglion nerve fibres leading into the optic nerve. There are approximately 126 million photoreceptors in the human retina of which about 6 million



c - cone r - rod
h - horizontal cell
b - bipolar cell
a - amacrine cell
M - Muller cell

Figure 3.1

Diagrammatic representation of the human retina

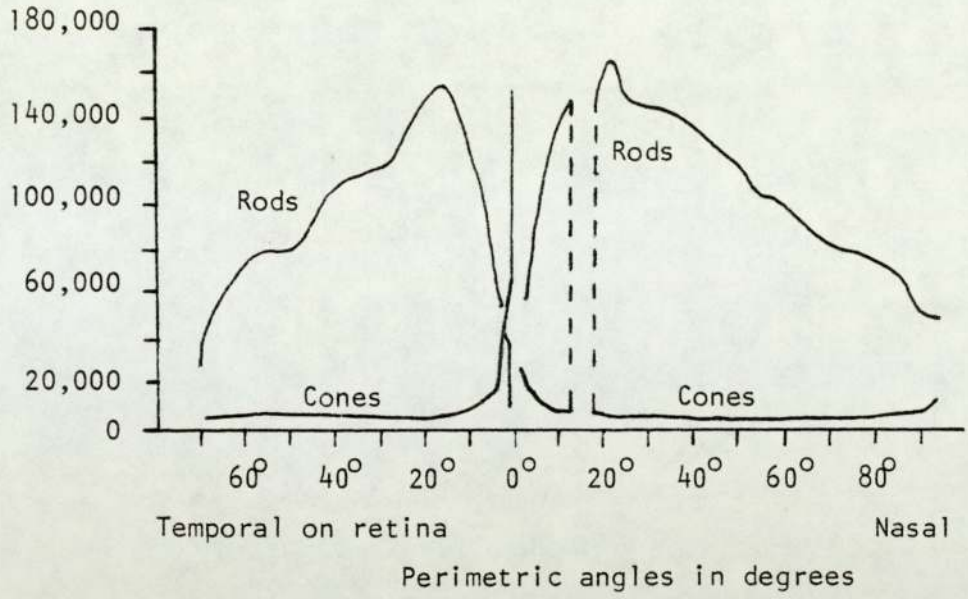
are cones (Adler, 1981). It is from the regional differences in the distribution of these photoreceptors that the differences in function between the central and peripheral regions have emerged.

The macula or central region of the retina (Figure 3.2b) differs considerably from the rest of the retina in its histology and is the area of high resolving power with a diameter of 5000-6000u and thus subtends about 15-20^{o} at the nodal point of the eye (Davson, 1972). The centre of the macula , the fovea centralis, contains only cones and the cones in this area are quite different in shape from those in the surrounding retina in that they resemble rods. This rod-free area corresponds to a visual angle of about 1^{o} and is the region of highest cone density and resolving power.

The number of cones decreases rapidly from the centre, falling to a low value in the periphery but rises again very slightly at the ora serrata. Outside the fovea centralis, the number of rods increases quickly, reaching a maximum of about 160,000 per mm^{2} at approximately 20^{o} from the centre (Figure 3.2a). In more peripheral areas, the number of rods decreases but remains considerably higher than the number of cones.

It is this variation in the distribution of the rods and cones which forms the basis for the duplicity theory of retinal function whereby the rod or scotopic system is more active in the periphery of the retina and is more effective at low light intensities whilst the cone or photopic system is more active in the central retina and is more effective at high intensities. This difference in the two systems is further enhanced by the fact that the macula is organised

(a)



(b)

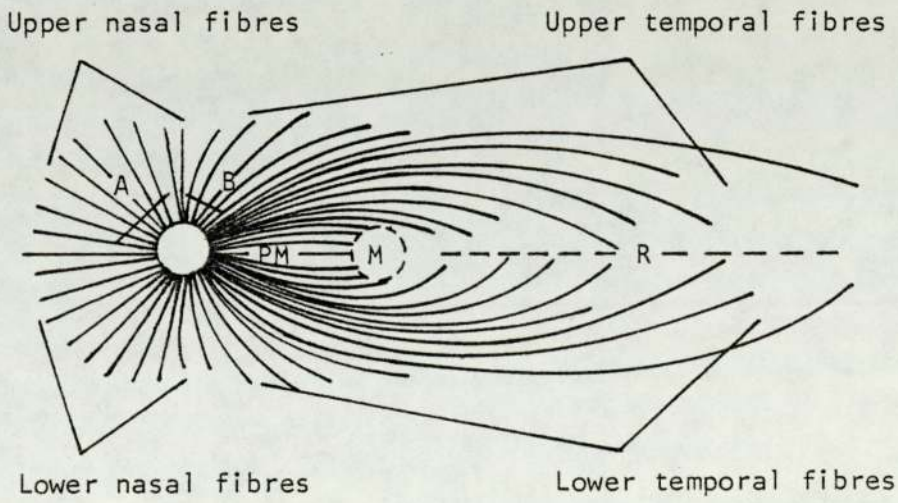


Figure 3.2

(a) Distribution of rods and cones in the human retina. Note that the distribution of rods and cones on the nasal side in and near fovea, not given on this graph, would be approximately the same as the distribution on the temporal side of the retina
(After Osterberg : from Pirenne, M. : Vision and the age, Pilot Press, London 1948)

(b) Schematized distribution of the left retinal nerve fibres. PM, Papillomacular bundle. M, Macula. R, Raphe formed by the termination of the upper and lower temporal quadrants. A, Lesion of upper nasal fibres. B, Lesion of upper temporal fibres.

so that each receptor may act as a unit, however as the periphery is approached, more receptors synapse with fewer ganglion cells. Therefore, the central receptive fields are small and present more finely processed information whereas the peripheral receptive fields are large and present a summed response of a much larger retinal area. Therefore, the centre of the retina is responsible for the encoding of fine spatial resolution and colour discrimination at higher intensity levels whilst the peripheral retina is highly developed to movement and is more effective at lower intensity levels. However, this is not to say that the two systems cannot overlap in their functions.

The arrangement of the ganglion nerve fibres as they enter the optic nerve head take on a characteristic formation which can be clearly demonstrated by considering lesions occurring in each set of fibres (Figure 3.2b). It can be seen that a lesion on the nasal side of the disc (A) would produce a fan-shaped visual field defect because of the arrangement of fibres whereas a lesion on the temporal side of the disc above the horizontal meridian (B) would result in an arcuate visual field defect (Figure 3.2b). The macular fibres form the papillomacular bundle which run from the fovea to the optic disc (the centre of the disc is situated about 15^{o} temporal and 1.5^{o} above the horizontal meridian when projected; its dimensions are about 7.5^{o} vertically and 5.5^{o} horizontally, Reed and Drance, 1972) in a compact bundle and damage to these fibres would result in a central or centrocaecal scotoma (Figure 3.2b).

The ganglion nerve fibres are further divided into two halves in relation to the centre of the fovea, that is, the temporal half and the nasal half, with the nasal half being larger (in man, 53% : 47% Kupfer et al. 1967). The nerve fibres for the temporal half remain

on the same side of the pathway in their course right up to the occipital cortex. On the other hand, the fibres from the nasal half, cross at the chiasma to enter in the optic tract of the opposite side right up to the visual cortex.

3.1 The Electroretinogram

The discovery of the corneo-retinal or resting potential by DuBois Reymond (1849) was a precursor to the discovery of the ERG by Holmgren in 1865. The ERG, which is a measure of the transient changes in the resting potential in response to light falling on the retina, was again independently reported by Dewar and McKendrick in 1873 with the former worker going on to record it in humans for the first time in 1877. Due to their slow recording techniques, these workers were only able to observe that there was a change in the retinal electrical potential of the vertebrate to the onset and offset of light. However, with considerable improvement in recording techniques, Gotch (1903) demonstrated a bi-phasic response consisting of a slight dip of negativity followed by a larger positivity to a single flash in frogs with his capillary electrometer whose deflections were photographed. Einthoven and Jolly (1908) went on to separate the response of the dark-adapted eye even further into an early cornea negative A wave, then a cornea positive B wave followed by a slower cornea C wave, as we still know them today. In some instances there was also a cornea positive D wave or off-effect (Figure 3.3). These investigators analysed the observed ERG into three components or processes whose successive electrical responses could be summated to produce the final waveform. Other workers such as Piper (1911), and Kohlrausch (1918) supported this view. Kohlrausch also

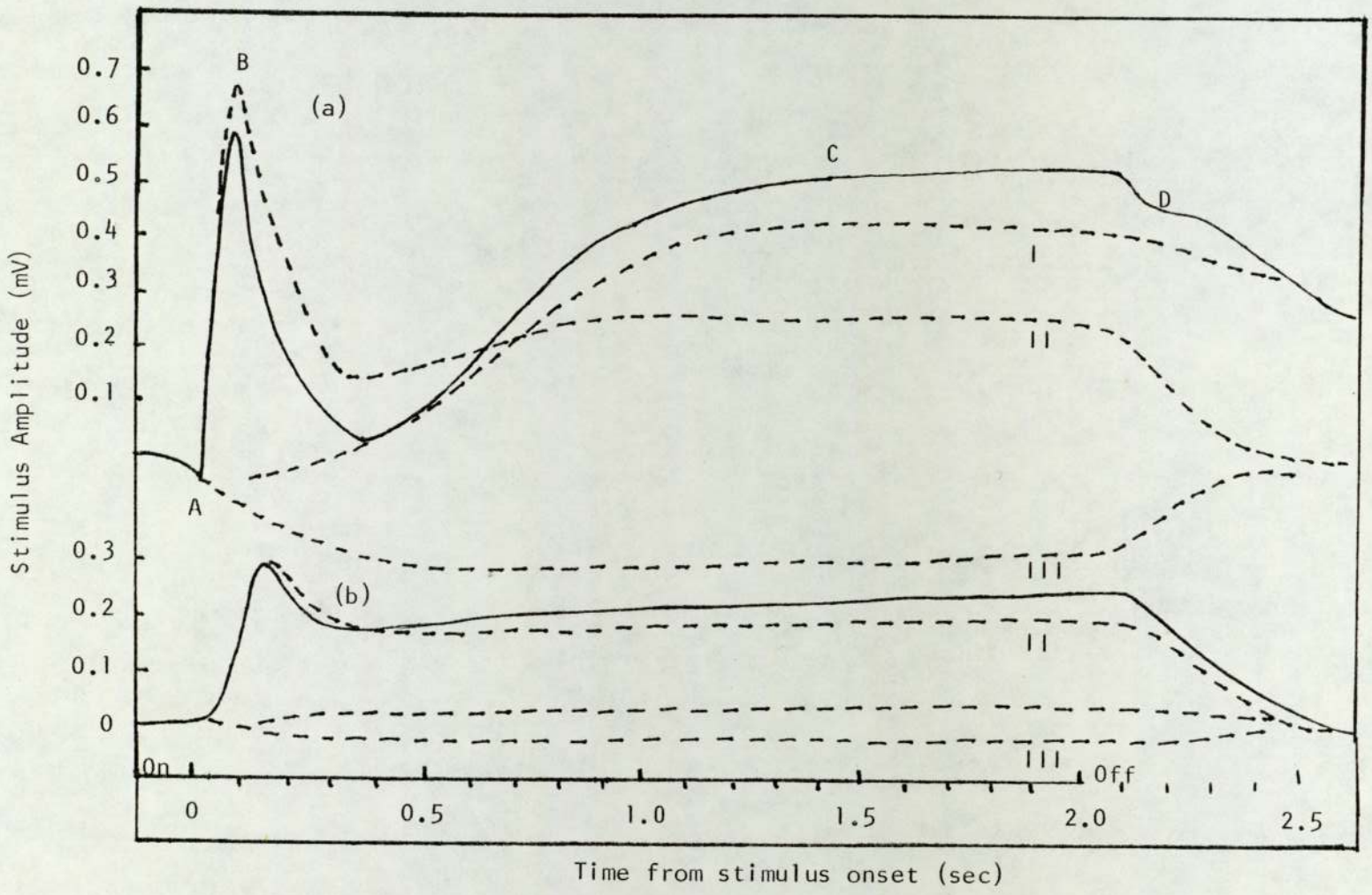


Figure 3.3

This diagram shows how the ERG may be analysed into three processes; PI, PII and PIII. They add together to produce an ERG with the A, B and C waves and an off-effect (D). The upper example (a) is an analysis of the response to a bright stimulus; the lower example (b) is for a dim stimulus. (After Granit, 1933).

found that mammals which demonstrated large A waves, also showed clear off-effects which led him to believe that these two waves were related in some way.

Many physiological studies have since been carried out on intact and excised retinae of invertebrates and vertebrates in an attempt to relate the components of the ERG to the various structures of the retina. The trend of the investigations has been to apply either biochemical methods to destroy specific groups of retinal cells, or electrophysiological methods whereby microelectrodes and the more modern micropipettes are used to observe the electrical response of several types of cells with or without the adminstration of chemicals. Granit (1932 and 1933) administered the first chemical agent with selective effects, namely ether, to the cat. He also used other chemical agents and methods, for example, anoxia, in his experiments. From the results of his experiments with ether at various illuminations, Granit identified three components, namely PI, PII and PIII which disappeared in sequence as the anaethesia deepened and he concluded that the ERG is a summation of these components (Figure 3.3). PI is largely responsible for the generation of the C wave, PII for the B wave and PIII for the A wave. Granit (1963) also realised that these components were dependent on stimulus intensity and on the type of retina stimulated. He classified the retinae into E and I retinae according to their functional properties whereby the E retinae showed less brisk effects than the I retinae, such as not being able to follow high frequency flickering stimuli. The E retina (found mostly in mammals) was predominated by rods whilst the I retina (birds, reptiles etc.) was predominated by cones. Hartline (1925) had earlier shown that the human ERG had a similar waveform to other vertebrates and that its size depended on stimulus intensity as in other species. He also

demonstrated that the size and waveform of the ERG were influenced by light adaptation and that the A wave became more prominent in light adapted conditions. This finding along with Granit's findings led later workers to believe that the A wave was dominated by cone activity.

As the characteristic waveform of the ERG became established, the more recent studies have concentrated on the origins of the individual waves and as a result of this, the ERG has been increasingly employed for clinical use. Firstly, the origins and characteristics of each wave will be discussed, starting with the A wave.

3.1.1 The A Wave (associated with the PIII component)

After Granit (1963) found that the PIII process, which is responsible for the generation of the A wave, was most resistant to ether and anoxia and it had a short implicit time, he concluded that this component was of photoreceptor origin rather than of neural origin. Pieron and Segal's findings (1939) supported Granit's conclusions when they found that the A wave was resistant to temperature changes. It had already been observed that the photochemical reactions of the receptors were unaffected by temperature changes.

Later workers continued to gather experimental evidence to examine this proposition. Noell (1954) performed a series of experiments whereby he produced an optic tract blockage by giving an iodoacetic acid injection to rabbits. He found that the A wave was most resistant and it did not disappear until a considerable number of receptor cells were destroyed by repeated injections of this chemical. He also blocked the central retinal artery causing the inner layers

to degenerate and on recording the ERG, the A wave was very prominent with the B wave being significantly reduced. On another occasion, he used pressurised oxygen to destroy the receptor cells and found a disappearance of the A wave. Potts et al. (1960) treated the retinae of newborn mice with sodium glutamate to produce retinae with pure receptor cells and they found that the ERGs consisted only of A waves. All this evidence suggested that the A wave is of photoreceptor origin.

Brown and Wiesel (1961a,b) and Brown (1968) performed micropipette recordings at different depths in the retina of the cat, when they determined at what depths the amplitudes of the A,B and C waves became largest. It was shown that the A wave is generated in a deeper or more distal layer than the B wave. Brown and Watnabe (1962) showed in the monkey, similarly to Noell, that by clamping the retinal circulation, the A wave remained whilst the B wave was abolished. The former workers also demonstrated a large A wave in the foveal ERG where there are mostly photoreceptors whilst in the peripheral regions where the inner nuclear layer is more prominent, the A wave decreased in amplitude and the B wave increased.

However, the A wave and the related PIII component were found to be more complex. Tomita et al. (1960) and Tomita (1963) in their microelectrode studies on the frog, found the A wave to be largest in the mammalian retinae, but Murakami and Kaneko (1966) went on to demonstrate with their own microelectrode technique on the frog, that PIII was divided into two fractions which they termed the distal and proximal PIII components which were recorded from the receptor layer and the inner nuclear layer respectively. Brown et al. (1965) associated this distal PIII component with the onset of the A wave in the monkey. The proximal PIII component has not been consistently

present in mammals (Brindley, 1970). Yonemura (1977) and Yonemura and Kawasaki (1978) demonstrated in the human eye that the latency and slope of the leading edge of the A wave coincides with that part of the PIII component which is referred to as the late receptor potential in warm-blooded animals. The remainder of PIII is modified by the superimposition of PI and PII. From the findings of these workers and those of Brown et al. (1965), it seems as if the A wave is initially generated by the distal PIII component in the receptor layer and corresponds to the late receptor potential.

On recording ERGs from the human eye, Armington et al. (1952) and Auerbach and Burian (1955) found that under suitable conditions, the A wave split into two cornea negative components. The former investigators demonstrated that the earlier component (Ap) had a spectral sensitivity function of the cone system and is hardly affected by light adaptation whilst the latter component (As) had a spectral sensitivity function of the rod system and is greatly affected by light adaptation.

3.1.2 The B Wave (associated with the PII component)

The origin/s of the composite B wave have also proved to be complicated. From 1954, Henkes reported that after central retinal artery occlusion occurred in humans, there was an abolition of the B wave whilst the A wave remained. As previously mentioned, other workers supported this finding (Noell, 1954; Brown and Watnabe, 1962; Gouras and Carr 1965).

Tomita et al. (1960) obtained electrical signals which were of similar

waveform to the B wave when they applied microelectrodes on opposite sides of the inner nuclear layer. This finding was upheld by Brown and Weisel (1961a,b) in the cat who observed that the B wave had its maximum amplitude when the electrode was placed in the inner nuclear layer. From the intraretinal recordings of these investigators, it was seen that the PII component was composed of two parts, namely 1) a transient positive peak superimposed on the rising phase of the response and 2) a more prolonged positive plateau of rectangular waveform, the direct-coupled (DC) component. These two parts behaved independently on varying the stimulus intensity whereby the transient component was markedly reduced at low intensities whilst the DC component remained. When recordings were carried out with external electrodes, the transient part contributed more to the B wave than the DC component. These two parts of PII (and hence the B wave) had maximum amplitudes in the inner nuclear layer (also Brown and Tasaki, 1961). Brown (1968) found that on using Xylocaine, which blocks the synapses of the photoreceptors and the inner retinal layers, the separate nature of the two parts of PII became evident when only the B wave was abolished and the DC component remained intact.

Miller and Dowling (1970) inserted micropipettes into a variety of retinal cell types of the mudpuppy and observed that with intracellular recording the Muller cell portrayed a similar latency and waveform to the extracellularly recorded B wave over a wide range of stimulus intensities, especially at the lower ones. The response from the Muller cell failed to give evidence of an A wave. The responses from the other cell types in the inner nuclear layer did not match the B wave.

From their observations and referring to those of Faber (1969), these workers concluded that a local depolarizing potential occurs in the Muller cell as a result of light-induced activity of the distal retinal neurones. This depolarization causes a radial flow of current through the retina which is recorded as the B wave. Similar to the sensitivity of the Muller cell to potassium ion (K^+) shifts in the rest of the nervous system, they postulated that the Muller cell may generate the B wave by a shift of the K^+ into the extracellular space between the nerve cells and Muller cells on light stimulation. The Muller cell also showed a positive off response similar to the off-effect of the ERG.

More recently, Dick and Miller (1978) and Kline et al. (1978) using potassium - sensitive electrodes in the retinae of the mudpuppy and skate respectively, reported two sites of K^+ shifts on light stimulation, one being in the region of the outer plexiform layer (distal) and the other in the vicinity of the amacrine cells (proximal). The accumulation of K^+ in the distal retina was faster and more transient than that in the proximal retina. Kline et al. proposed a model to explain how the current flow in the extracellular space along the Muller cell gives rise to the B wave (Figure 3.4).

On referring to Figure 3.4 , the sites at which the K^+ are released into the extracellular space by active neurones are at the interface of regions I and II/II and III. At these sites, called current sinks, the current flows into the Muller cell producing the current paths shown by arrows in the diagram. On considering the B wave as a transretinal potential, then the contribution to the B wave from the proximal current sink is comparatively negligible (because at the site

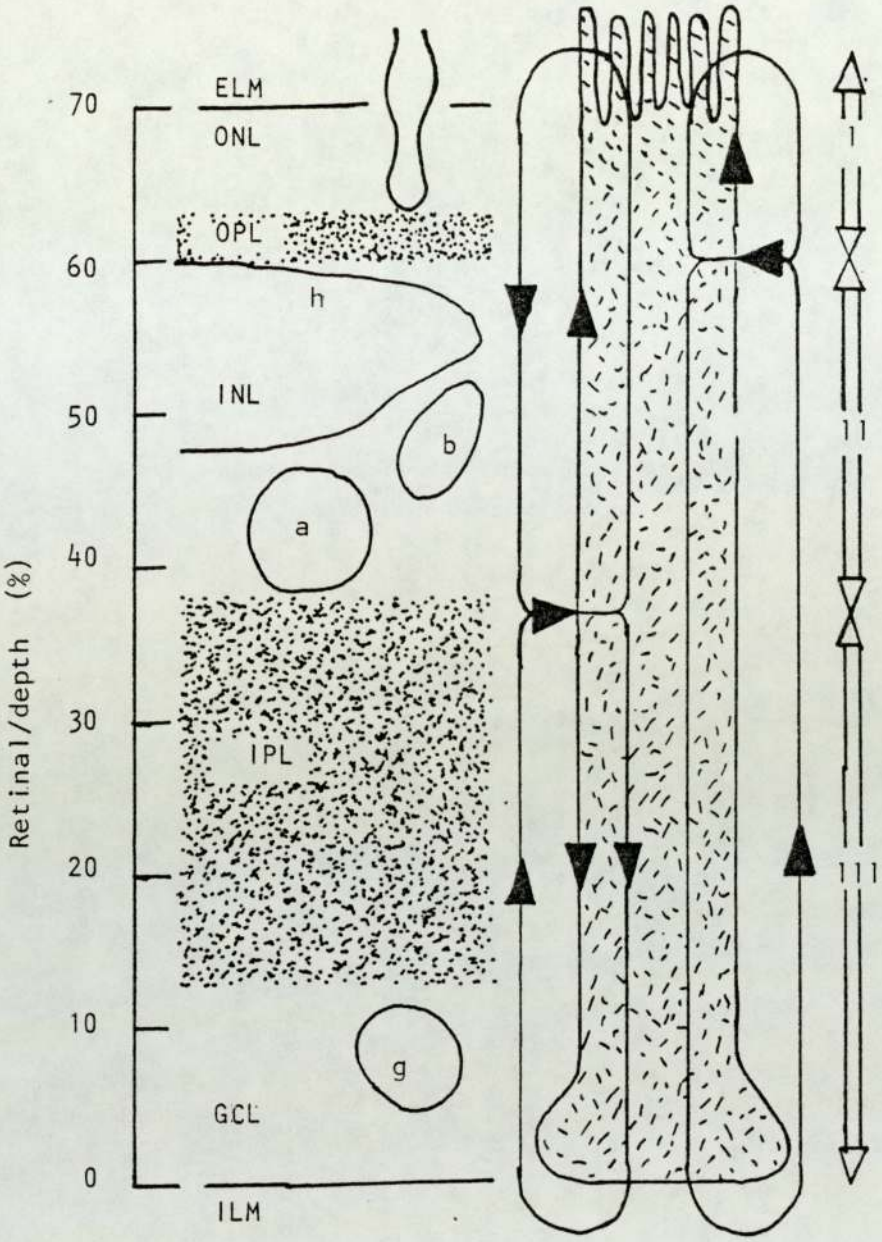


Figure 3.4

Drawing of the skate retina (70% retinal depth corresponds to about 105um). The Muller cell (stippled) extends from the internal limiting membrane (ILM) at the vitreal surface of the retina to the external limiting membrane (ELM) in the outer nuclear layer (ONL). Proposed current flow set up around the Muller cell is indicated by arrows. There is a distal current sink at the interface of regions I and II and a proximal current sink at the interface of regions II and III. Cell types: g, ganglion; a, amacrine; b, bipolar; h, horizontal; r, receptor; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer

(After Kline et al. 1978)

midway along the Muller cell, there are two current paths of opposite polarity and nearly equal magnitude) whilst the contribution from the distal current sink is substantial as it is asymmetrically positioned along the Muller cell, therefore giving rise to the B wave. These workers have postulated that the efflux of K^+ in the distal retina is initiated by the activity of the depolarizing bipolar cells.

Vogel and Green (1980) felt that the above hypothesis would lead one to expect sinks of B wave current where the K^+ concentration is elevated. However, in their microelectrode study where local ERGs and K^+ concentrations were simultaneously recorded (in the Rana pipiens) they found that the spatial and temporal development of B wave current sinks was not identical to that of the extracellular K^+ increase. These workers suggested that if the Muller cell plays any role in the B wave generation, then it must be in conjunction with other retinal cells.

Szamier et al. (1980) applied two chemical agents to the skate retina which selectively interfered with the structural integrity of neuroglia. The first drug resulted in suppression or loss of the B wave with gross histological changes in the Muller cells, especially in the inner retinal layers and in some amacrine cells. Surprisingly, there was recovery of the B wave in spite of persistent damage in the Muller cells. This evidence would again indicate the involvement of other cells in the generation of the B wave. The other drug produced a greater effect on all ERG components and more extensive cellular damage.

Although the B wave is supposed to be of non-neural origin, it has been shown that it is a meaningful measure of retinal excitability in light stimulation.

Dowling (1964) found that after exposing the rat's retina to bright light, the log threshold of the B wave was linearly related to the rhodopsin content of the rods. It was also shown that rats who were on a vitamin A deficient diet and therefore showing reduced levels of rhodopsin, gave ERGs in which there was an increase in the log threshold of the B wave. This experimenter (1970) examined the retinal activity of the skate under light and dark adaptation conditions, when a close similarity was seen in the behaviour of the B wave and ganglion cell activity.

Similar to the A wave, it has been demonstrated that the B wave has separate contributions from the rod and cone systems. Motokawa and Mita (1942) showed that the B wave consisted of a pointed positive X wave followed by a rounded B wave proper with red stimulation. Adrian (1945) observed that in stimulus conditions which favoured cone activity, the B wave was small in amplitude and of short latency whereas in stimulus conditions which favoured rod activity, the B wave was of large amplitude and longer latency. Johnson and Cornsweet (1954) carried out an experiment under conditions of complete dark adaptation and steady white light adaptation. In the former case, the peak sensitivity of the B wave to single flashes was about 505nm. and in the latter case, the peak sensitivity shifted to about 555nm, therefore portraying the Purkinje shift.

The spectral sensitivity curves in the monkey of the three cone mechanisms were also obtained by using the B wave. Narrow band stimuli were superimposed on different bright coloured backgrounds depending on which cone mechanism was to be optimally stimulated, e.g. a purple background was used when the sensitivity curve of the middle wavelength

(green) was to be plotted. The intensities of the backgrounds were such that any rod activity was eliminated (Padmos and Van Norren, 1971; Mehaffey and Berson, 1974).

3.1.3 The C wave (associated with the P1 component)

In his series of experiments, Noell (1954) showed that by selectively destroying the pigment epithelium with an intravenous injection of sodium iodate, the C wave was greatly reduced. More recently, Imaizumi et al. (1972) observed with their electron microscope that after a single large dose of sodium iodate was injected into the rabbit, changes were initially seen in the pigment epithelium and outer segments of the receptors, but afterwards the inner layers were also affected. They also gave small continuous doses for a period and found changes in the outer segments of the receptors and to a lesser extent, in Bruch's membrane and the pigment epithelium. It is difficult to compare the two sets of experiments because of their different methods of administration. However, Noell only reported destruction of the pigment epithelium after six weeks to a relatively small dose.

Nakajima (1958) injected the rabbit with aminodiphenoxyalkane drugs which attack the pigment epithelium. After a few days, the ERG had disappeared. He explained this by saying that since the receptor cell outer segments cannot function when the pigment epithelium has been destroyed, then secondary degeneration of the photoreceptors occurs eventually and therefore there can be no ERG.

Granit and Munsterhjelm (1937) had earlier reported that the dark

adapted C wave had a spectral sensitivity curve which matched the absorption spectrum of rhodopsin and not that of melanin in the pigment epithelium, indicating that the rods contribute or lead to the response. From the results of the last three investigators, it appears that the generation of the C wave required the complementary functioning of the pigment epithelium and the rods.

In spite of the shortcomings of experiments with chemical agents, the microelectrode studies also indicated the pigment epithelium as the site of origin of the C wave. Brown and Tasaki (1961) recorded the maximum amplitude of the C wave from the pigment side of Bruch's membrane. Steinberg et al. (1970) carried out intracellular recordings within the pigment epithelium of the cat and the responses produced had a similar waveform and latency to the C wave.

Riggs and Johnson (1949) and Pearlman (1962) suggested that the C wave may have a pupillociliary origin since it is substantially reduced by the administration of miotics and mydriatics.

3.1.4 The D wave or Off-effect

The earlier workers (Holmgren, 1865; Dewar and McKendrick, 1873 and Gotch, 1903) had noticed a change in the retinal potential when a flash or light went off. This was believed to be the result of interference between the A, B and C waves. It was also observed that whenever the A wave was of large amplitude, there was also a good off-effect. It was postulated that the PIII component (A wave) of the ERG is a preparation for an off effect during illumination and that the off effect is a sort of release from inhibition due to the return

of PIII to the baseline (Granit, 1963).

Kawasaki and Jacobson (1971) studied the off-effect in detail in man and found that with weak stimulation the off effect is of negative polarity and is associated with rod activity whilst with higher intensities, the off effect becomes positive and is associated with cone activity. It was also noticed that the negative off effect was absent in congenital stationary night-blindness whereas the positive off effect was present, but in patients with rod monochromatism, the inverse situation occurred.

In the clinical use of the human ERG, the C and D waves have not gained as much importance as the other components, perhaps because they require longer duration stimuli for their generation than is normally employed (that is > 20ms). The electrooculogram and the C wave also overlap in their representation of retinal activity of the pigment epithelium.

With great advances in microelectrode and recording techniques, two other components of the ERG have been discovered. They are: 1) the early receptor potential (ERP) and 2) the oscillatory potentials (OP).

3.1.5 The Early Receptor Potential (ERP)

Brown and Murakami (1964) obtained an electrical response of extremely short latency when a microelectrode was inserted into the inner segment of the photoreceptors which did not appear to be the A wave because of its short latency. Cone (1964) demonstrated that the stimulus intensity needed to obtain the ERP is about 10^6 times higher than

that required for the rest of the ERG. In the human, it occurred within 1.5ms of stimulus onset. The ERP is of a biphasic waveform with the initial small positive phase (RI) followed by a larger negative phase (RII) which leads into the leading edge of the A wave (Galloway, 1967; Carr and Siegel, 1970).

Cone (1965) found that the amplitude of the ERP was directly proportional to the amount of unbleached rhodopsin in the rods of the rat's retina. However, Goldstein and Berson (1970) and Carr and Siegel (1970) showed that the ERP was cone dominated (60-80% of total amplitude) in humans although rhodopsin is the predominant visual pigment.

One explanation for the cone dominance of the ERP is that many cone disc lamina are continued with the vitreous and hence the cornea, whilst most of the rod outer segments are surrounded by a plasma membrane and therefore shielded from the vitreous and cornea. The displacement of charge in the "unshielded" cone lamina could explain the cone dominance in the ERPs of humans and monkeys (Berson, 1981).

Cone and Brown (1967) and Brown (1968) found that the ERP disappeared at the same temperature at which the visual pigment molecules lost their regular orientation and about 95% of the response was photolabile. It was suggested that the ERP is generated in the outer segments of the receptors because of its immeasurable latency, as well as its correlation with the accumulation of specific photoproducts of bleaching. The ERP was thought to be due to the movements of charge in the visual pigment molecules.

For the ERP to be elicited under clinical conditions, a flash gun has

to be used in conjunction with maxwellian viewing to maximise the stimulus intensity. The photoelectric and electric artefacts have to be eliminated by using a suitable contact lens electrode and masking the equipment properly. The ERP has been found useful in detecting retinitis pigmentosa (Berson and Goldstein, 1970), although it is most resistant to anoxia and even death of tissues (Brown, 1968).

3.1.6 The Oscillatory Potential (OP)

Cobb and Morton (1952) were the first investigators to obtain the "E waves" or oscillatory potentials (as they are now called) in humans to high intensity flashes. They have also been referred to as humps (Bornschein and Goodman, 1957), multiple components (Heck and Rendahl, 1957) and Y waves (Aoki, 1960). They consist of a series of rapid rhythmic wavelets superimposed on the B wave and have been recorded in many species (Yonemura, et al. 1963; Brown et al. 1965 and Brown, 1968). Brown et al. (1965) postulated that the OPs must arise from cells proximal to the receptor cells because their amplitudes (as well as the B wave) diminished on recording from the fovea in comparison to the peripheral retina of the monkey. When the retinal circulation was clamped, recordings from both fovea and periphery showed that the OPs and B wave were abolished again indicating that the OPs arise in the inner part of the retina (Brown, 1968).

Brindley (1956) found the maximum amplitude of the OPs to be in the inner nuclear layer of the frog which was supported by Yonemura and Hatton (1966), but Brown (1968) reported the maximum amplitude as coming from another region of the retina.

From their histological studies, Yonemura et al. (1963) suggested that the appearance of the wavelets had some relation to the inner nuclear layer as they were more distinct in animals where this layer was thick, e.g. in humans and pigeons this was also observed by Algvere (1968).

Doty and Kimura (1963) found that in cats and monkeys, antidromic stimulation of the optic nerve fibres did not reset the rhythm of the OP's and the OP's were still present in optic atrophy (Yonemura, 1962), suggesting that the ganglion cel ls were not the pacemaker for these wavelets. Ogden (1973) reported that the first 3 OPs in the monkey demonstrated maximum amplitudes in the inner plexiform layer. He proposed that the axon terminals of bipolar cells, amacrine cells and the dendrites of ganglion cells could be responsible for the initiation of these wavelets. Wachmeister and Dowling (1979) found that the OPs reversed in polarity at different depths of the mudpuppy's retina therefore reflecting radial flows of current in the retina. However, they did not find that the tangential flows of current from the amacrine cells which extend laterally, showed any reverse in polarity during electrode penetration, indicating that the origin of the OPs is not in the amacrine cells. The earlier OPs were seen to arise more proximally in the retina than the later ones, suggesting that the OPs may represent feedbackloops of synaptic origin as they were abolished by GABA (gamma-amino-butyric-acid).

Yonemura et al. (1979) administered intravitreally glycine, B-alamine, taurine and GABA in monkeys and rabbits and obtained a reduced amplitude of the OPs. They applied antagonistic drugs to release the suppressive effects of the above drugs when the OPs were restored.

This evidence again pointed to the assumption that the OPs are related to the neuronal network.

The variation in the possible origin/s of the OPs was commented on by Brown (1968) who also felt that the OPs probably depend upon neural feedback circuits which could differ between species.

There is considerable evidence which indicates that the OPs and the B wave have separate origins and behave differently under identical experimental conditions and in certain diseases. Yonemura (1962); Yonemura et al. (1962); Ikeda and Friedmann (1972); Ikeda (1976) reported that the OPs disappeared or were greatly diminished or even delayed (Yonemura and Kawasaki, 1979) in many cases of diabetic retinopathy, even though the A and B waves remained normal and the retinopathy was slight or not visible with an ophthalmoscope. Simonsen (1968) reported hyper-normal OPs in longstanding diabetics without visible retinopathy but diminished OPs in patients with bad visual prognosis.

Algvere (1968) and Stangos et al. (1970) also found the OPs to be more sensitive than the B wave in other retinal vascular diseases (hypertensive retinopathy, Eales disease etc.). Therefore, the OPs are very vulnerable to any interference in the retinal circulation and synaptic transmission within the retina.

All these findings indicate that the OPs and B wave can be affected separately and are not produced by the same processes. On the other hand, it seems that their generation depends somewhat on the processes which generate the B wave.

There have been conflicting accounts on the contribution of the scotopic and photopic mechanisms in the appearance of the OPs Jacobson et al. (1966); Stangos et al. (1970); Algvere and Westbeck (1972); Babel et al. (1977) supported the notion that these wavelets are cone-dominated for a number of reasons, such as, they are elicited by strong light; they become prominent when a stimulus is repeated if the light was not intense enough to produce distinct OPs with a previous flash, especially as dark adaptation progresses; they are present at mesopic levels of light adaptation; they are most prominent in cone-dominated retinae, for example, turtle pigeon; they disappear in most cases of rod monochromatism and achromatism whilst they are retained in nyctalopia. However, Watnabe et al. (1973) and Watnabe and Toyama (1979) postulated that these wavelets originate as an interaction of both the scotopic and photopic systems as they could be recorded in rod and cone dominated retinae. They found that the spectral sensitivity curves of the OPs reflected scotopic as well as photopic character in several animals.

In humans, Fujimura et al. (1972) observed OPs of maximum amplitude between 500 and 600nm in the light adapted eye. Stodmeister (1973) and Wachmeister (1974) recorded under light and dark adaptation conditions and found that the spectral sensitivity curves matched the photopic and scotopic curves accordingly, indicating interaction of the rod and cone systems. Korth (1980) obtained the spectral sensitivity of the B wave and the OPs as the eye passed from dark to light adaptation. He found that the wavelets first appeared at adaptation levels associated with mesopic activity. The spectral sensitivity of the wavelets corresponded closely with the curve of the peripheral cones, therefore reflecting photopic activity. He suggested the conflict in the results of the previous workers as possibly due to differing experimental conditions for their monochromatic flash stimulation, for example, intensity of adapting light which was controlled in his experiment by using

pattern reversal stimulation etc.

Korth and Reiman (1979) had earlier reported about the presence of two wavelets, called S_1 and S_2, under scotopic conditions and four wavelets (O_1 - O_4) under photopic conditions. They suggested that S_1 and S_2 were of a separate origin to O_1 - O_4 (which were all seen on the rising slope of the B wave) as the amplitude and time interval between the two scotopic waves did not depend on stimulus intensity, they were of lower frequency than the photopic wavelets and S_2 was seen on the falling slope of the B wave.

As mentioned previously, the number and morphology of the OPs superimposed on the B wave depend largely on stimulus conditions. The number of OPs increases and their peak time decreases with increasing stimulus intensity (Bornschein and Goodman, 1957; Heck and Rendahl, 1957; Babel et al. 1977). Denden (1978) showed that if the intensity of the adapting light increases then the stimulus intensity must also become more intense to produce the same number of OPs.. The amplitudes of the OPs also alter with differing interstimulus intervals (Algvere and Westbeck, 1972; Wachmeister and Dowling, 1979). It has been shown that the morphology of the OPs changes with differing frequencies (rising on the B wave with increased frequency) but their periodicities remain fairly stable (Yonemura, 1962; Babel et al. 1977). This former worker, as well as Alfieri and Sole (1968) found that OPs were more easily recorded with red stimulation rather than with blue stimulation, once more suggesting the predominance of the photopic mechanism.

Heck and Rendahl (1957) observed that different OPs disappear in various forms of colour defectiveness, especially on pre-adaptation to

coloured stimulation, therefore, postulating that the three colour mechanisms contributed differentially to each wavelet. However, Fujimura et al. (1972) failed to disclose any variation in colour sensitivity of the individual OPs. Ponte and Anastasi (1978) reported normal OPs in protan and deutan defects with the OPs being abolished only in achromatopsia.

3.1.7 Clinical Electroretinogram

From the above account, it can be seen that many studies have been carried out in order to examine the origins and nature of the components of the ERG and as years have passed, the investigating techniques have been greatly improved, therefore yielding more accurate results. Nevertheless, there are still some questions which require clarification and further research is being carried out for this reason. This is not to say that the ERG does not provide useful clinical information about the function of the retina because it has already been proved to be a helpful diagnostic tool in many diseases, for example, vascular diseases, the effects of drugs on the eye etc. (Babel et al. 1977; Galloway, 1981).

The ERG, recorded externally at the cornea to full-field flash stimulation is a massive response from the processes of the whole retina. The main components of the ERG are the A and B waves and special conditions have to be used to reveal the others. Gouras (1966) demonstrated that there is a summation between the retinal scotopic and photopic activity by recording internally from the peri-fovea of the monkey under two conditions. The scotopic responses were obtained to a dim blue light (419nm) which all began with the stimulus whilst the photopic responses were obtained to a deep red light (672nm) with the stimulus being

progressively delayed in this case. When the two stimuli were presented in the same time intervals as before, they were found to algebraically summate under all conditions.

Berson et al. (1969) supported this finding in humans when they showed that under different coloured stimulation, the ERGs from the normal subject represented the algebraic sum of the ERGs from a patient with night blindness and from a patient with rod monochromatism.

Armington (1968) presented various test stimuli (2^{o} - 12^{o}) at different luminances under photopic conditions and recorded the amplitude of the B wave. For a given field size, an increase in luminance also caused an increase in the B wave until a maximum amplitude was attained. At a constant luminance level, the amplitude of the ERG was proportional to the area of the retinal image of the stimulus over a wide range. This was explained in terms of the additivity of the ERG and it was found that the amplitude was proportional to the number of cones stimulated (also Brindley, 1970; Lawwill et al. 1977; Armington and Brigell, 1981).

From evidence previously mentioned, it is realised that the type of ERG obtained depends largely on the stimulus conditions and the adjustment of the parameters of the recording equipment. The factors which influence the ERG are listed below:

A Physiological and Psychological Factors

1) State of adaptation
2) Pupil size
3) Age
4) Sex

5) Refractive changes

6) Intra-individual changes, including diurnal rhythms

7) Training

B Stimulus conditions and parameters of the recording equipment

1) Intensity, colour and frequency of test stimulus

2) Duration and rate of onset of stimulus

3) Filter settings and gain settings on the amplifier

4) Electrode positions

C Causes of artefact in response

1) Blinking and eye movements

2) Tears

3) Bubbles in contact lens electrode

4) Photoelectric and electrical artefacts.

First the physiological factors will be discussed as given in (A)

1 State of Adaptation

As already stated, the waveform of the ERG changes under different conditions of light and dark adaptation. On employing suitable conditions, the A and B waves can be seen to split into two parts with the earlier part predominating under photopic conditions and the latter part predominating under scotopic conditions (Motokawi and Mita, 1942; Adrian, 1945; Armington et al. 1952; Auerbach and Burian, 1955).

With increased dark adaptation, the amplitude of the B wave increases and its shape becomes more rounded. Although the changes in the A wave are not as obvious, this wave is seen to augment during dark adaptation.

2 Pupil Size

Francois and De Rouck (1961) and Karpe and Wulfing (1961) investigated the effect of pupil size upon the A and B waves and various levels of illumination. They found that the maximal amplitude of the B wave was obtained at different intensity levels with each pupil size, but when the pupil was larger than 5mm, the B wave attained its maximum value at the same intensity. Before the peak had been reached, they obtained a linear relationship. This indicated to them that at low intensities, the amplitude of the B wave is dependent on the pupillary area whilst at high intensities, the B wave remains more or less unchanged. The A wave never attained a maximum amplitude with increasing intensity. The CFF values as monitored by the amplitude of the B wave were also altered by pupil size.

From previous evidence, it can be seen that the latencies of the ERG components are also affected by increasing intensity which could be partially due to changes in pupil size. However, if normative data is obtained for persons in similar age groups, this should not be such a problem except in cases where the person's pupil size falls outside normal limits. In addition to this, if the test is performed in a darkened room (when the pupil dilates to a constant aperture) the error should be negligible. When high intensity flashes are used, then the electric response occurs before the undilated pupil reacts (Galloway, 1981).

3 Age

Zetterstrom (1956), employing Karpe's technique detected an ERG in the

human newborn 1 - 3 days after birth when a small slow positive wave (B wave) was seen. The A wave began to appear after 6 months whilst a decrease in latency was always occurring in the B wave. At one year, all the waves could be seen in the correct proportion, although the amplitudes were still reduced. With different recording techniques and high intensity flashes, Horsten and Winkelman (1960, 1962) obtained an ERG, consisting of the A and B waves shortly after birth. They also demonstrated cone activity by obtaining responses to high flash rates. Algvere and Zetterstrom (1967) later found OPs in the newborn's ERG under special conditions.

After the first year, the ERG seemed to alter little until about 60 years old when a sharp decrease in amplitude was observed (Zeidler, 1959). Karpe et al. (1950) and Peterson (1968) also described a decline in the amplitude of the B wave with increasing age. Straub (1961) reported a decrease in amplitude in both the A and B waves and an increase in the latency of the B wave.

Weleber (1981) recorded the ERG under light and dark adapted conditions and reported that the amplitudes of the scotopic B wave, the mesopic 'Bx' wave and the photopic B wave were all significantly age dependent (that is, the amplitude decreased with age). However, no significant age correlation was found for the amplitude of the dark adapted cone A wave , the scotopic A wave, the mesopic A wave or for any of the implicit times. However, it was mentioned that with more data, there might have been a small positive correlation between implicit times and age.

Martin and Heckenlively (1982) recorded photopic, scotopic and dark-adapted bright flash ERGs. For the photopic ERG they found that in both

sexes, there was a decrease in A and B wave amplitudes and an increase in the B wave implicit time with increasing age. For the scotopic ERG (only the B wave was analysed), there was a significant age effect on the B wave amplitude with the B wave implicit time just failing to reach significance. For the dark-adapted bright-flash ERG, significant age effects were seen for the A and B wave amplitudes and implicit times.

4 Sex

Vainio-Mattila (1951) and Peterson (1968) both found that women had significantly higher B wave amplitudes than men ranging from 19-50 years old and 10-69 years old respectively. The latter worker suggested that this was due to the shorter eyeball lengths in women, therefore increasing the intensity of light on the retina. Zeidler (1959) found a higher B wave amplitude in women only in the 31-50 age group.

Martin and Heckenlively (1982) reported significant differences between the sexes for the A and B wave amplitudes and implicit times in the photopic and dark adapted bright flash ERGs. For the scotopic ERG, there was only a significant difference for the B wave implicit time.

5 Refractive changes

Karpe (1945) noticed that the amplitude of the components of the ERG were reduced in three out of four high myopes whom be examined. Peterson (1968) reported that the B wave amplitude was lower in myopic (-1D; the difference being greater in this group) and hypermetropic women (+ 2.25D) than in the normal group (-1D to +2D) and lower in myopic men but higher in hypermetropic men. No conclusions were drawn

as the numbers of eyes in the myopic and hypermetropic groups were small.

6 Intra-individual differences, including diurnal rhythms

Karpe (1945) described a change of 6% - 15% in the B wave amplitude of fifteen subjects from one session to another over several months. Spivey and Pearlman (1963) observed changes from 16% to 95% in 19 trained subjects. However, this could be because they expressed it as a percentage of the smallest response obtained, therefore exaggerating the variation. Peterson (1968) also showed a variation of 5% to 15% of the normal B potential over several years (up to 5 years), testing at approximately three monthly intervals.

Ronchi and Ercoles (1968a) reported that the B wave amplitude altered periodically during the course of the day with each cyclic variation period lasting from 90 - 120 minutes. However, this period is quite short compared with the diurnal variation in humans. In another study on two subjects (1968b), they found that in one of them, the B wave amplitude was smaller during the morning than in the afternoon whereas in the other subject, the converse was seen.

Peterson (1968) found that the mean difference in the amplitudes of the B wave (the mean of B potential in the right eye minus the B potential in the left eye) between the right and left eyes of 171 persons was very small. Karpe (1945) suggested that the difference in the B potential between the two eyes should be more than 25% before it is denoted as being pathological.

7 Training

It has been suggested that training has an effect on the ERG. Ronchi and Freedmann (1964) presented 25-30 flashes to subjects after which time, a neutral density filter was used to decrease the stimulus intensity by about 1 log unit. Only 2 or 3 flashes were given at this intensity and then the stimulation was again presented at the original intensity. It was found there was no significant difference in the ERGs between the three conditions which they claimed was due to training. However, Armington felt these results could be explained by other means, such as the relative independence of the B wave amplitude at high intensities.

B Stimulus conditions and parameters of the recording equipment

1 Intensity, colour and frequency of stimulation intensity

Already it has been stated that with an increase in stimulus intensity, there is a decrease in the latencies of the components of the ERG and an increase in the amplitude of the A and B waves (Adrian, 1941). With increasing intensity whereas the A wave continues to become more prominent, the B wave reaches a maximum value and then begins to decrease (that is, if the peak is measured from the baseline; Burian and Pearlman, 1964); the OPs also decrease in latency, but they maintain their periodicity (Babel et al. 1977).

Colour

The colour of stimulation can play a role in maximally activating different visual mechanisms in that blue stimulation favours rod

activity and red stimulation favours cone activity (Motokawa and Mita, 1942; Bornschein, 1959; Babel et al. 1977; Weleber, 1981). Babel et al. (1977) found that with red stimulation, the OPs were well developed and it was very sensitive in pathological cases.

Mehaffey and Berson (1974) reported that the ratio of the blue : green : red cones in the dark adapted cone ERG is 1:6.5 : 5.4. They separated the cone systems by using different coloured adapting fields. The differences in the ERG spectral sensitivity to 25 and 50Hz flickering stimuli were explained by a summation of the blue cones to the red and green cones at the lower frequency. This indicated to them that the three cone mechanisms acted independently in generating the cone B wave in response to a large test stimulus.

Frequency

The frequency of occurrence of the light stimulus produces a change in the waveform of the ERG. Adrian (1945) employed various flicker rates with white and coloured stimuli. He proposed that with slow blue flashes; the rod system would be preferably activated whilst with the faster red flashes, the cone system would be preferably activated and that flicker would produce a better separation than single flashes. He was proved to be correct because blue stimulation produced a single, rounded response whereas green and orange red stimulation produced a double response indicating rod and cone activity. The cone B wave was seen best with red stimulation and could follow at flicker rates greater than 15Hz whilst the rod B wave disappeared at approximately 3Hz. With the longer wavelength stimuli with a double response, the second rod component became very small, almost leaving the cone component alone. Dodt (1951) stated that at slow flicker rates, the ERG waveform was

completely developed, but at higher rates, a subsequent flash started before the response to the preceding flash was finished therefore cancelling out the slower components.

Johnson and Cornsweet (1954) and Armington and Biersdorf (1956) demonstrated that with frequencies of 20Hz and more, the spectral sensitivity curve matched the photopic psychophysical curve. At higher flicker rates, the response becomes more pointed leaving the photopic B wave. Many subsequent workers and clinicians have used higher flicker rates (20-25Hz) to separate the cone and rod system (Berson et al. 1969; Mehaffey and Berson, 1974; Babel et al. 1977).

It should be mentioned that even when the full ERG is recorded, its waveform is altered with increasing stimulus frequency. The appearance of the OPs is also affected by stimulus frequency (Heck and Rendahl, 1957; Babel et al. 1977; Wachmeister and Dowling, 1979).

2 Duration and rate of onset of stimulus

Duration

Biersdorf (1958) observed the effects of different duration times and stimulus intensities on the human ERG which consisted of an A wave, scotopic and photopic B waves. He employed exposure times ranging from 250us to 500ms and found that the A and photopic B waves adhered to the Bunsen-Roscoe law (luminance x time = constant) fairly well whereas the scotopic B wave was the summation of many processes. It was pointed out that its measurement was difficult to certain intensities and the effect of stray light could not be dismissed. The optimum duration

of the stimulus was about 25ms for the photopic B wave at all intensities and 10 to 25ms for the A wave.

Wachmeister (1976) found that when short interstimulus intervals were used, the threshold of the OPs was determined by the light intensity. At longer interstimulus intervals and with weak light adaptation, the threshold was dependent on intensity and duration of the stimulus, that is, temporal summation was taking place.

Rate of onset

Bornschein and Gunkel (1956) conducted experiments on the rise times of stimuli and showed that the A wave was greatly reduced by increasing the rise time from 25ms to 100ms with the B wave remaining stable. With a further increase from 100ms to 280ms, the A wave was eliminated and the B wave was increased in latency.

3 Filter and gain settings

Adjustment of the high pass (time constant, TC) and low pass filters, determines the bandwidth of each recording channel. The low pass filter is often used to eliminate interference from the main supply or high frequency random noise. However, there are times when one wants to record only high frequency components of the ERG, for example, the OPs in which case the time constant is made shorter and the low pass filter is increased. The waveform of the ERG is altered at different filter positions (see Cooper et al. 1980, for a more detailed description). For general clinical purposes, a TC of 0.3s or 0.5s is used.

The sensitivity of a system (expressed in uV/cm) is the magnitude of input voltage required to produce a standard pen deflection. This depends on two factors, that is 1) the gain of the amplifier (EEG machine) and 2) the sensitivity of the pen writer. The gain of an EEG amplifier is large and necessitates several stages of amplification. It is expressed as the ratio of the output voltage to the input voltage.

4 Electrode position

The position of the reference and active electrodes have been shown to produce a change in the amplitude of the ERG. The maximum amplitude is at corneal sites, gradually diminishing as the active electrode moves off the limbus and out of the eye (Sundmark, 1959; Rubinstein and Harding, 1981). Rubinstein and Harding (1981) found that the A wave disappeared earlier than the B wave as the distance between the cornea and active electrode increased, however the latencies remained very similar for the various positions. They obtained a high correlation between the A and B wave amplitudes and latencies for the gold leaf electrode and the Henkes contact lens electrode. These workers also employed different reference electrode locations and did not find any appreciable effect on latency or amplitude of the ERG, although there was an increase in myogenic artefact at the anterior neck reference.

During recording, the positions of the active and reference electrodes should be kept as constant and symmetrical as possible for each subject so that the size of the response will not markedly alter.

C The causes of artefact

The effects of blinking, eye movements, excessive tearing, bubbles in the contact lens electrode produce a poorer response. The patient should be warned that on the onset of flashes he should try and avoid excessive blinking, eye movements or other muscular activity.

Both the electrical and photoelectric artefacts have to be eliminated if the ERP is to be obtained.

3.1.8 Electrode Types

The development of suitable electrodes for clinical recording of human ERGs provided quite a challenge. Hartline (1925) fitted himself with a pair of tightly fitting goggles filled with a conducting solution and an electrode placed inside. This was not very successful as the solution eventually leaked out. Riggs (1941) produced the first contact lens electrode which remained in place making good fluid contact with the eye and was less abrasive to the eye. Contact lens electrodes are still used today and many workers have produced their own, employing both scleral (Karpe, 1945) and corneal forms (Burian-Allen, 1954). Other electrode types have been used such as a ring of gold foil placed on the cornea. Although it gave reasonable responses, it was difficult to use as the cornea had to be kept wet and the subject prevented from blinking all the time (Ziv, 1961). The idea of a gold leaf electrode has been taken further and an extremely thin gold-coated mylar leaf was formed to fit into the lower fornix under the cornea, therefore providing a better fit on the patient's eye with no disturbance of the optics of the eye and less ocular irritation. This electrode can be

used for extended wear and in persons with corneal pathology (Borda et al. 1977; Arden et al. 1979). Another type of electrode has been developed which offers the same advantages as those of the gold leaf electrode. This electrode (DTL electrode, Dawson et al. 1979) is based upon an extremely low mass conductive thread which makes contact between the tear film of the eye and an adjacent stranded, insulated electric wire. The thread which consists of 3 to 6 nylon fibres is impregnated with metallic silver.

Standard EEG disc electrodes can be used, especially on young children when the active electrode is placed near the canthi or lids.

3.1.9 Use of the ERG for Clinical Purposes

Many workers have now developed their own clinical techniques for recording the ERG with the knowledge of the influencing factors upon the ERG and of the types of conditions which have to be employed to demonstrate certain components.

Karpe (1945) described in detail his clinical techniques which were time-consuming, but provided a guideline for other clinicians. Since that time, each clinic has developed its own technique using various dark adaptation periods, various intensities, colours, frequencies and types of stimuli etc. With the advent of the computer in the 1960's the automatic averaging technique has made the recording of all evoked potentials much easier with a vast improvement in the signal/noise ratio, that is extracting and enhancing small weak, but time-evoked signals from the background noise (Jacobson et al. 1962; Armington, 1974; Babel et al. 1977; Galloway, 1981).

It is not within the scope of this thesis to describe the different clinical conditions under which the ERG is recorded in each laboratory (see Babel et al. 1977; Galloway, 1981 for more details). However, it should be said that for clinical purposes, the ERG can be obtained under certain conditions which activate the rod or cone systems or a combination of these systems. The ERG to white light in a dark adapted retina reflects rod and cone activity; however a photopic ERG can be obtained by the following methods:

1) Flickering stimulus - a flicker photopic stimulus at a frequency of 25-30Hz is used
2) Surround illumination - the stimulus, consisting of alternating black and white stripes, is surrounded by a steady intense illumination of the peripheral retina - a steady blue suppresses the activity of the scotopic system without unduly affecting the photopic receptors (Brindley and Westheimer, 1965)
3) Red filter - a deep red filter (say Kodak Wratten, No 26) is used with photopic intensities as the scotopic system is relatively insensitive to red (Stangos et al. 1970; Babel et al. 1977)

A scotopic ERG can be produced by stimulating with a deep blue filter (say Kodak Wratten No 47B) at low intensities after dark adaptation which is below the cone threshold.

In 1970, at the Meeting of the International Society of Clinical Electroretinography, Gouras suggested that an electronic flash or tungsten light could be used as a stimulus in conjunction with ganzfeld stimulation to provide full-field stimulation. This type of stimulation

allows homogeneous stimulation of the retina and avoids the effects of unequal illumination which occurs when stray light is present.

In spite of the fact that the ERG as presently recorded represents a massive response from the entire retina, some workers have been able to produce a foveal ERG which is small in amplitude and requires computer averaging to elicit it. Arden and Bankes (1966) and Biersdorf and Diller (1969) used a small red flickering stimulus (4^{o}) surrounded by a large background (50^{o}) sufficient to eliminate the scotopic contribution. Prior to stimulating the fovea, the effects of stray light had to be accounted for. This method is used to detect macular degeneration. A hand-held ophthalmoscope has been designed on the above principles in order to produce foveal and parafoveal ERGs (Sanderg et al. 1977).

The ERG has been thought to be a response to a change in luminance flux on the retina and although patterned stimuli have been previously used (Riggs, et al, 1964), to maintain a constant level of retinal light adaptation, they have not been used for their spatial properties. More recently, certain workers have reported that an ERG which responds to various sizes of pattern elements can be obtained (Lawwill et al. 1977; Sokol and Bloom, 1977; Nelson et al. 1979; Diehl and Zrenner, 1980; Groneburg, 1980; Arden et al. 1980; Halliday and Mushin, 1980; Armington and Brigell, 1981; Fiorentini et al. 1981).

Nelson et al. (1979) found that in the cat, the B wave was seen to be sensitive to diameters of spots and widths of bars when the area of retina stimulated was kept constant. As the spot diameters and hence the spot separations increased, the B wave amplitude decreased until

it was abolished and only a negative component (PIII) was left. Defocussing of the pattern showed a return of the B wave. A pattern-specific model was focussed in terms of the centre-surround structure of the ERG generators in the inner nuclear layer (Figure 3.5). When fine spots were used (a), they illuminated the centre-surround structure evenly but dimly and the response obtained was similar to dim diffuse illumination producing ERGs of long implicit times and larger amplitudes. The B wave was abolished when the spot diameters and separations were such that the surround was left in the dark and only the centre was well stimulated (b). With further increases in spot diameter, the spots stimulate the surround but with less receptive units being hit, thus in the fine spot pattern, giving rise to a B wave of smaller amplitude and shorter implicit times as the receptive units that are stimulated receive much more illumination.

Diehl and Zrenner (1980) applied this concept to humans. They designed a circular spot pattern arranged in concentric circles (subtending 85^{o}) according to the change of the perceptive field size in man with increased eccentricity. They found that on focussing the pattern, there was a 33% decrease in the A and B wave amplitudes in comparison to the defocussed state. For the maximum amplitude change to occur between the focussed and defocussed states, a coarser pattern had to be used than anticipated from the perceptive field data, which suggested to these workers that retinal receptive field sizes might be more extended than cortical perceptive field sizes. Armington and Brigell (1981) also found that the ERG responded best to coarser patterns at all retinal locations up to 21^{o}. The ERG was also larger when central stimulation was included (also Lawwill et al. 1977).

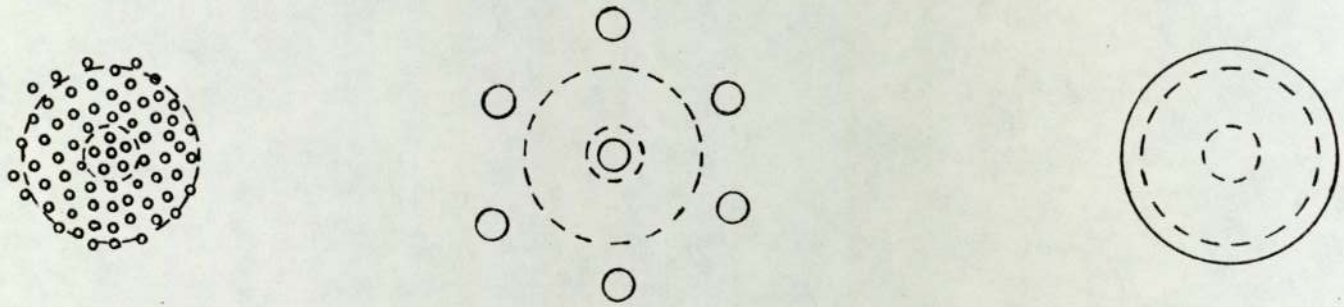


Figure 3.5

Principal model relating to ERG responses elicited by fine (A), medium (B), and coarse (C) spot patterns to the receptive fields of the ERG-generators (represented by the broken lines as a concentric centre-surround structure). It is suggested that the B-wave is abolished only if the surround (annular region between dotted circles) is kept in the dark (B).

(After Nelson et al. 1979).

Arden et al. (1980) had found that with pattern reversal checkerboard stimulation, the ERGs from amblyopic eyes (stimulating corresponding retinal areas) were 50% or less of the response from the fellow eye (maximum interocular difference in normals was 10%), especially in those who failed to respond to treatment. On occluding the area of amblyopic suppression, there is no change in the response from the amblyopic eye, but there is a reduction in the fellow eye, leading these workers to believe that there is very little electrical activity from the amblyopic eye. Although they were unsure of the cell generating the response, they felt that their results gave support to the hypothesis of the peripheral origin of amblyopia. In their carefully controlled experiments, Spekreijse et al. (1973) and Reimslag et al. (Personal Communication) concluded that the ERG was the net result of luminance changes and was not pattern-specific because the waveform of the ERGs to pure luminance stimulation and pattern reversal stimulation (using various check sizes) were very similar at low and high frequencies. The latter workers found that the ERG waveform was not markedly altered when an equiluminant red-green checkerboard pattern was changed to a homogeneous red-green exchange, maintaining the same chromatic contrast..

However, Arden et al. (1980) produced conflicting results as their ERGs at the same contrast produced different waveforms depending on whether the stimulus field lacked or contained a pattern. The patterned stimulus field gave a small amplitude ERG and a faster implicit time of the cornea positive component than the unpatterned stimulus. On reducing the contrast of the unpatterned stimulus to give a similar amplitude to the ERG of the pattern stimulus, they were still of completely different waveforms. This discrepancy between Spekreijse

et al. and Arden et al. cannot be explained by Nelson et al's. model as both experiments used checks of the same size (1^{o}). It is unlikely that the differences in field size (8^{o} and 30^{o}, Spekreijse et al; 16^{o} Arden et al.) could change the waveform of the ERG so dramatically.

Fiorentini et al. (1981) recorded ERGs to alternating grating patterns, flashes of light and flickering lights in 8 patients with unilateral temporary occlusions of the retinal artery, retrobulbar neuritis, optic atrophy and chronic glaucoma. They found that the ERGs to alternating gratings were absent or depressed whereas the ERGs to light flashes and flickering light were normal. They also found a difference in amplitude between the normal and affected eye at various spatial frequencies. They postulated that the pattern ERG is correlated with ganglion cell activity. However, the findings of Sherman (1982) suggest that the pattern ERG is of pre-ganglionic origin as it was normal in optic nerve disease, but reduced in macular disease.

No latency changes were reported in any of the above studies with pattern reversal stimulation which might have been expected to occur in some of the conditions studied, for example, optic atrophy, if these ERGs are associated with ganglion cell activity. As the amplitude of these ERGs are so small (about 3uV), a large number of sweeps is required to elicit them.

3.2 THE VISUAL EVOKED RESPONSE

3.2.1 Brief Description of the Organisation of the Fibres and the Types of Cells in the Visual Pathway.

Now that the function and the application of the ERG have been presented, it is appropriate to discuss these aspects in relation to the VER. First of all, however, some reference will be made to the organisation of the visual fibres and the types of visual cells which have been discovered. As the organisation of the fibres in different regions of the visual pathways would require a detailed and long explanation (refer to Wolff, 1976), it is felt that the most concise and clear way of representing these pathways is by a diagram showing the abnormalities in the visual fields caused by partial or total interruption of the nerve fibres at progressive levels. (Figure 3.6). Figure 3.7 & 3.8 represent the schematic cortical projection of the visual areas in man.

There is a general localisation of retinal fibres in the striate area (area 17) which is the visuosensory area of the cortex. Fibres from the corresponding upper retinal quadrants terminate in cells above the calcarine fissure and fibres from the corresponding lower retinal quadrants terminate in cells below the fissure, that is the upper visual field is represented below the calcarine fissure and the lower visual field is represented above the calcarine fissure (Figure 3.7). The macula is represented in a large posterior portion of area 17, that is the occipital pole. On progressing from the macula to the more

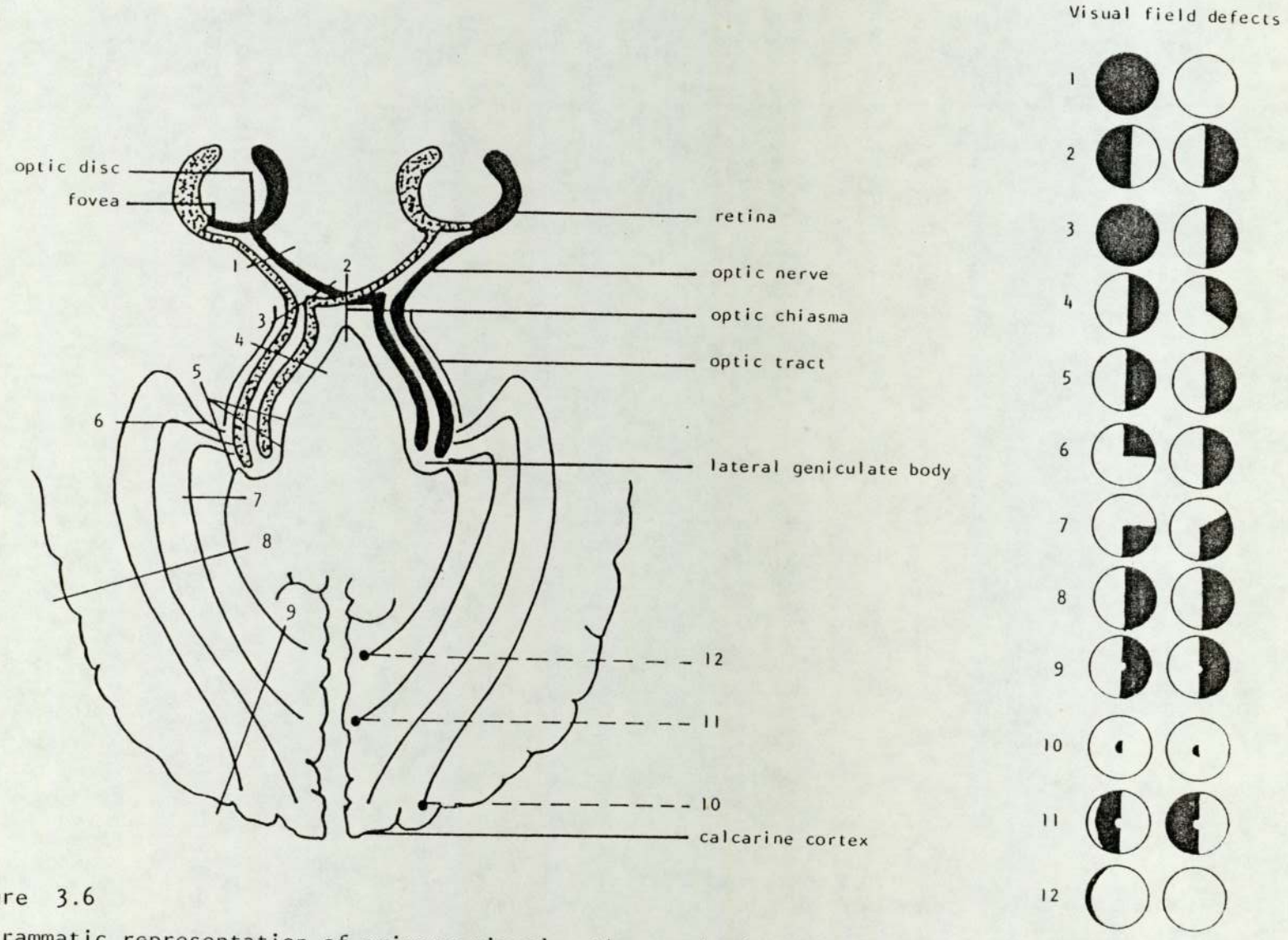


Figure 3.6

Diagrammatic representation of primary visual pathway, showing in schematic fashion abnormalities in visual fields produced by discrete and total interruption of nerve fibres at various levels. Visual fields are shown as viewed by the patient, with black areas indicating areas of absent vision. (After Harrington, 1976)

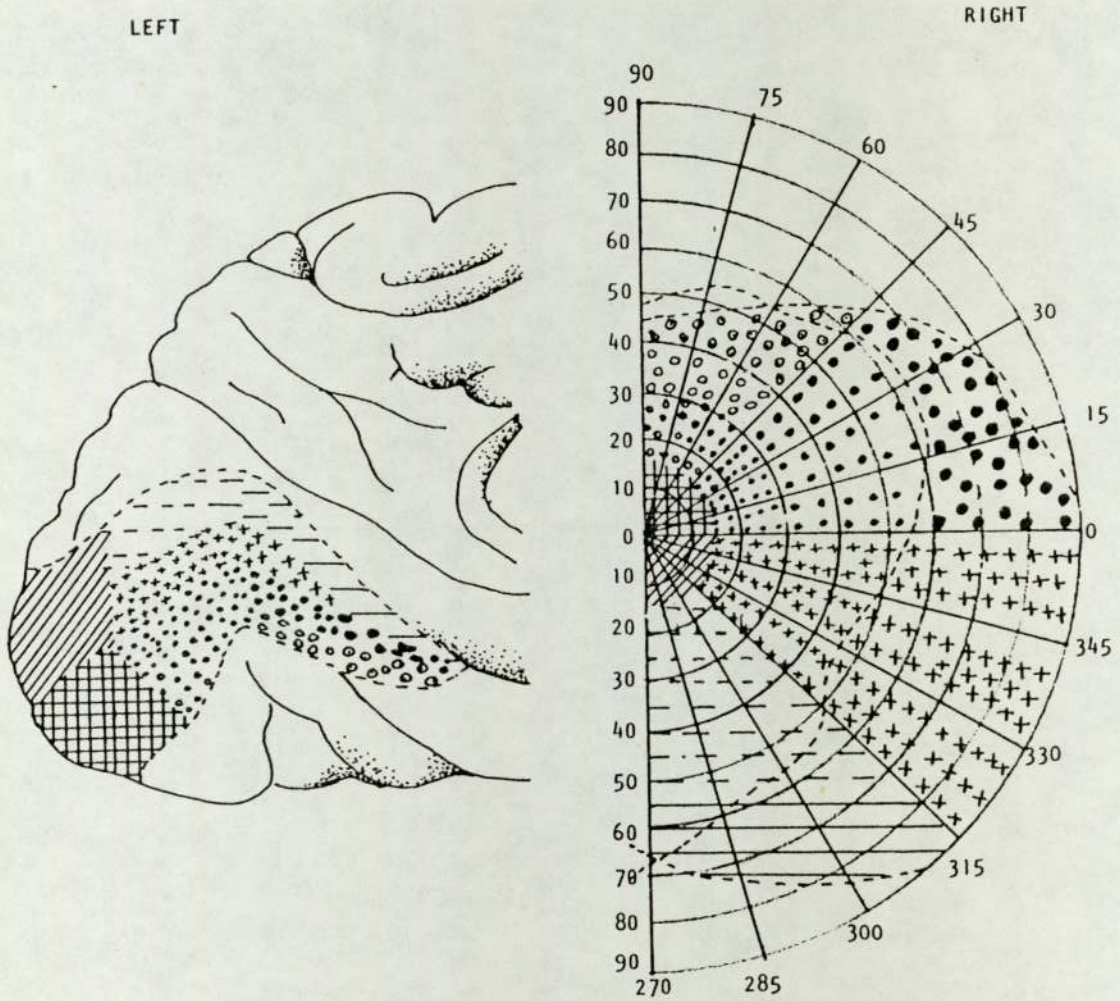


Figure 3.7

Diagrammatic representation of the right visual field on the calcarine fissure of the left hemisphere in humans. Calcarine fissure is widely opened. Symbols on cortex indicate representation of that part of visual field containing the symbols (after Holmes, 1945)

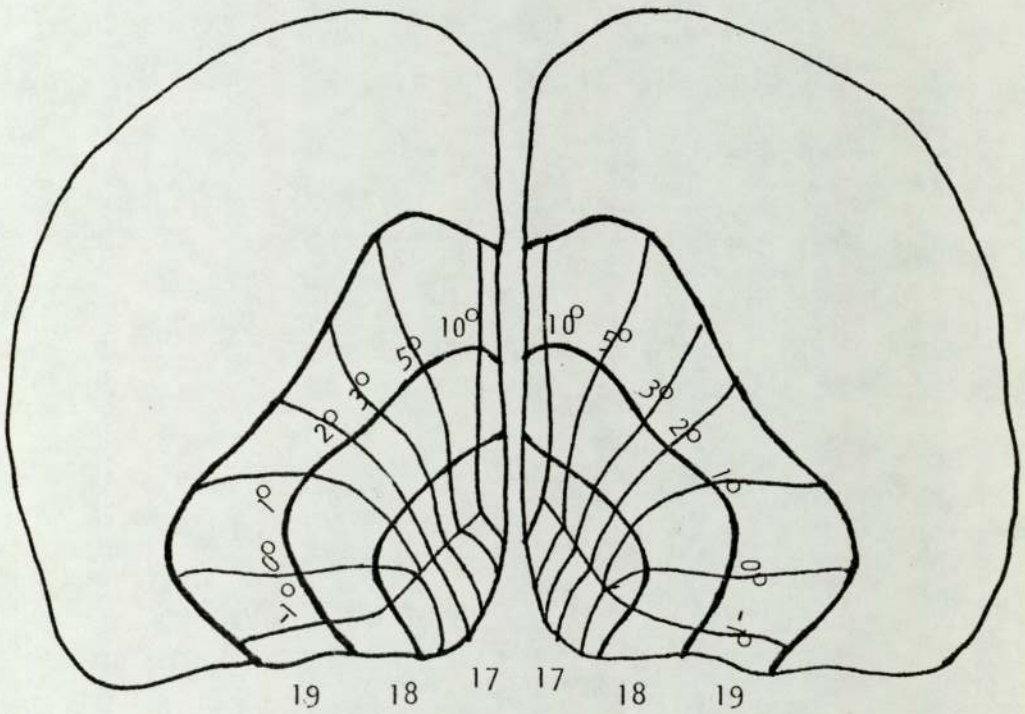


Figure 3.8

A schematic cortical projection of the visual areas in man. Finer lines represent constant eccentricity in the visual field. (After Drasdo 1980)

eccentric retinal areas, the further away from the occipital pole will the representation of each area be found. (Figure 3.7).

Outside the striate area (area 17) and closely following its contours are two other areas which are concerned with visual reactions and are the parastriate (area 18) and peristriate (area 19) areas, Figure 3.8). It is observed that the visual fibres of area 17, continue into areas 18 and 19 which are thought to be visuomotor and visuo-psychic areas respectively (Adler, 1981).

An important point should be made at this stage as it is very relevant to the generation of the VER. From Figure 3.7, it can be seen that central vision is represented in an area of the cortex which is quite large relative to more peripheral vision. For example, in the monkey, about one-third of the surface of the primary visual cortex is devoted to the central 5^{o} (Daniel and Whitteridge, 1961). Relating this to the VER, it has been shown that on stimulating various retinal locations on the horizontal and vertical meridians (with a 2-5^{o} spot), the ratio of the VER form each retinal site to that from the fovea was already substantially decreased on a retinal location of as little as 5^{o} from the fovea. (Copenhaver and Perry, 1964).

The discovery of several types of visual cells and fibres in more recent years has contributed to further understanding of how the visual neural system operates and has helped to explain which types of cells are maximally activated by various forms of stimulation in visual psychophysics and electrophysiology. With this information in mind, it might be found that a certain type of stimulation is more effective in the early detection of a certain disease.

The experiments on the nerve cells and fibres began with Hartline (1938) when he recorded three types of optic nerve fibres in his microelectrode studies on the frog. They were:- 1) the "on" fibres (continue to discharge during illumination); 2) the "on-off" fibres (only respond at the onset and cessation of illumination) and 3) "off" fibres (responding only to the cessation of light). He also introduced the term "receptive field", which was described as the area of a single fibre or cell which responds to the onset or cessation of a spot of light.

In 1953, Kuffler found that by moving a spot of light to different positions in a ganglion cell of the cat's retina, he could demonstrate that each receptive field consisted of concentric zones. The circular central zone of higher sensitivity possessed either "on" or "off" responses whilst the surround annular zone showed antagonistic responses to those of the centre.

In an investigation employing sinusoidal gratings to examine the centre-surround nature of the cat's retinal ganglion cells, Enroth-Cugell and Robson (1966) were able to distinguish between two types of cells, that is the X and Y cells. Their evidence suggested that linear summation (that is, the signal is altered by a fixed factor without altering the frequency) occurred in the X cells whilst non-linear summation occurred in the Y cells.

Cleland, et al. (1971) showed that the firing rate of some of the ganglion cells showed a sharp increase followed by a decrease but

never returning to the baseline whilst the stimulus was present, that is, the sustained cell. However, there were other cells which showed a sharp increase on presentation of the stimulus but quickly returned to the baseline, that is, the transient cell. The sustained cells also demonstrated longer retinogeniculate conduction times than the transient cells. These cells were said to correspond to the X and Y cells respectively.

Rowe and Stone (1977) and Lennie (1980) cautioned that not all X cells portray sustained responses and not all Y cells portray transient responses. It also depended on other factors, for example, all cells become more sustained on dark adaptation and more transient in the peripheral retina.

A study of the spatial and temporal contrast sensitivity in areas 17 and 18 (which contain a predominance of X and Y cells respectively) of the cat's cortex, showed that there was a marked drop in contrast sensitivity at low spatial frequencies for the X cell whilst the Y cell failed to do this. It was postulated that the preference of the X cells to relatively high spatial frequencies (and narrower bandwidths) and low and moderate temporal frequencies gave them an advantage for pattern discrimination whilst the preference for relatively low spatial frequencies and high temporal frequencies favoured reactions to movement. (Ikeda and Wright, 1975; Movshon, et al. 1978).

There is another type of ganglion cell which has been observed in the cat's retina, namely the W cell. For the properties of the

three types of retinal ganglion cells found in the cat, see Table 3.1. In the rhesus monkey, Gouras (1969) and De Monasterio et al (1976) classified the ganglion cells into two types, namely: 1) the phasic cell which gave a transient response to maintained stimuli, and 2) the tonic cell which discharged continuously to maintained stimuli and which were more common near the fovea where small ganglion cells predominate although both cell types were found adjacent to each other. Whereas most tonic cells demonstrated colour opponency, the phasic cells did not show this (Gouras 1972; De Monasterio, 1978).

In the striate cortex of the rhesus monkey where the receptive fields are not concentric, the cells have been placed in three groups, that is simple, complex and hypercomplex cells according to their properties. Although all of these cells respond best to line stimuli (bars, slits or edges) in a particular orientation, surprisingly the simple cell is more discriminating than the complex cell as to the exact position of the stimulus in the receptive field. These three types of cells demonstrate colour specific properties. (Hubel and Weisel, 1968; Michael, 1978 a and b; 1979). The cortical cells with simple receptive fields can combine to stimulate the complex receptive fields (Hubel and Weisel, 1962). These cells allow a detailed analysis of the various attributes of a stimulus.

3.2.2 History and Development of the Visual Evoked Response

The discovery of the VER was due to the observations and recordings made by many scientists which lead to the revelation of the electro-

TABLE

	Y CELLS	X CELLS	W CELLS
Receptive field centre size	Large, 0.5 to 2.5 degrees	Small, 10 min of arc to 1 degree	Large, 0.4 to 2.5 degrees
Linearity of centre-surround summation	Nonlinear	Linear	Not tested
Periphery effect	Present	Usually absent	Absent
Axonal veloctiy	Fast, 30 to 40 m/sec	Slow, 15 to 23 m/sec	Very slow, 2 to 18 m/sec
Soma size, peripheral retina	Large, > 22 um	Medium, 14 to 22 um	Small, < 15 um.
Proportion of population	<10%	Approx 40%	Approx 50% to 55%
Retinal distribution	Concentrate near area centralis, more numerous relatively in peripheral retina.	Concentrate at area centralis	Concentrate at area centralis and in streak.
Central projections	To laminae A, A_1, and C of LGN, to MIN and via, branching axon, to SC from the A laminae of LGN to cortical areas 17 & 18. also by branching axon; from MIN to areas 17,18 & 19	To laminae A, A_1, and C of LGN. thence to area 17, to midbrain (a minority), but probably not to SC	To SC, to C laminae of LGN; thence to visual cortex area 17 and/or 18 & 19.

continued/over

Table continued

	Y CELLS	X CELLS	W CELLS
Nasotemporal division	Nasal cells project contralaterally; most temporal cells ipsilaterally; strip of intermingling centred slightly temporal to area centralis.	Nasal cells project contralaterally, temporal cells project ipsilaterally; narrow strip of intermingling centred on area centralis.	Nasal cells project contralaterally, most temporal cells also project contralaterally; about 40% of temporal cells project ipsilaterally.
Responses to standing contrast	Phasic or transient in most cells; some are tonic or sustained especially near area centralis; all are tonic when dark adapted.	Most give tonic responses in mesopic conditions, many are transient when light adapted.	Either tonic or phasic.
Receptive field "layout"	On-centre/off-surround or off-centre on-surround	Same as for Y cells	Some have same layout as Y and X cells, others have on-off centres, some have purely inhibitory centres, some are directionally selective or colour coded
Morphologic correlates	α Cells	β Cells	γ Cells

Table 3.1 Some properties of cat retinal ganglion cells.

(After Rowe, M.H., and Stone, J. 1977).

encephalogram (EEG) and eventually to the VER. As early as 1791, Galvani noticed that when a nerve or muscle was injured, a current flowed from the outer uninjured surface to the injured surface. Matteucci (1838) and Du Bois Reymond (1849) went on to establish the "muscle" and "nerve" currents respectively with the latter investigator eventually showing that the steady potential difference between the undamaged and damaged surfaces of a nerve trunk could be altered by stimulating the nerve. He termed this "the negative variation". Caton (1875) then tried to find out if this negative variation in demarcation potential could be shown in the brain by stimulating any of its sense organs. In fact, he not only demonstrated this but also observed that when his two electrodes were placed on uncut cortex (hence eliminating the demarcation current), there were continual fluctuations of current even when all experimental stimulation of the animal had ceased. He called these, "the electric currents of the brain", which is in effect, the EEG. This worker also demonstrated responses to photic stimulation in animals and applied special techniques, such as hypoxia and anaesthesia, to prove the biological origins of these rhythms. In 1890, Beck, unaware of Caton's findings produced his thesis on action potentials in the brain when it was activated by impulses initiated in its sense receptors.

With the invention of the vacuum tube the small electrical responses which were formerly just recordable could now be amplified and studied in detail. In spite of this, some workers still remained sceptical about these potential changes in the brain and thought that they were just artifacts of muscle movement (Tchiriev, 1904).

Berger (1929) was able to show that these electrical rhythms also occurred in man. He initially recorded a 10Hz alpha rhythm on eye closure which disappeared on eye opening. He also noticed that the EEG was abnormal in epileptics. The findings of two subsequent sets of workers have remained the framework of diagnosis in electroencephalography until today, that is the discovery of the spike and wave discharge in epilepsy by Gibbs et al. (1935) and the association of the slow delta waves with brain tumours (Walter, 1936).

The change in the EEG from slow, high voltage to fast, low voltage activity when the subject is presented with visual stimuli was studied in detail first by Adrian and Matthews (1934) and then by Jasper and Cruickshank (1936). They showed that responses following regularly repeated flashes of light could be recorded from the occipital cortex. This was the beginning of the development of the response which we now call "the visually evoked cortical potential (VECP), or "the visual evoked response (VER)". The VERs which were recorded by these workers could not be used clinically as they were more often masked by the general EEG activity.

Galambos and Davis (1943) and Dawson (1947) later invented a technique of isolating the VER from the background EEG whereby an oscilloscope was triggered simultaneously with the presentation of a stimulus and the waveform was photographed each time. The photographs were superimposed to observe the consistency of the waveform.

Later, Dawson (1951) devised the first computer which modified the superimposition technique by having the responses time-locked to the onset of the stimulus at regular intervals. This lead to the advent of improved computers in the 1960's which revolutionised the recording of evoked potentials, whereby

an averaging technique is used to elicit them. By employing an analogue to digital converter, each time the stimulus is presented, the evoked response is added together in a digital form and divided by the number of stimulus presentations (n) therefore improving the signal to noise ratio by a factor of $\sqrt{n}$. However, this technique assumes that each response is time locked to the onset of the stimulus, therefore slowly reinforcing the coherent portions of the responses to produce a clear signal whilst the background activity of the EEG is presumably non-coherent, therefore tending to cancel out. However, time-locked EEG activity, for example alpha activity can interfere with the clarity of the signal; nevertheless this can be often overcome by arousing the subject. In spite of this disadvantage, the signal to noise ratio has been greatly improved by the use of this method.

Workers who have been involved in describing the components of the VER, have used lower frequencies of stimulation (< 4Hz). Most of the work has been devoted to the measurement of latencies and amplitudes of the different components. The classification of the components of the VER recorded to flash stimulation at the occiput by Ciganek (1961) and subsequent workers (Gastaut and Regis, 1967; Dustman and Beck, 1969; Goff et al 1969; Harding, 1974), has received much attention (Figure 3.9). It can be seen that the classification system includes numerals, letters, etc. but in this project, the notation used by Harding, (1974) will be adopted whereby there is an indication of the polarity of the deflection or component. The VER recorded by Ciganek (from O_2) proceeded from Wave I at 50 ms to Wave VII at 220 ms. This author separated

the VER into primary (first three waves up to 90 ms) and secondary (>90-240 ms) components and a rhythmic after discharge. He suggested that the primary components originated in the striate cortex (area 17); the secondary components in area 18 and possibly 19 and the after discharge could not be attributed to a specific cortical origin.

The occipital scalp responses to diffuse light stimulus have been reported to show considerable intra- and inter- individual variability (Cobb, 1950; Pampiglione, 1953; Werre and Smith, 1964) but averaging has greatly helped to reduce this variability and fairly high correlations have been observed for the VER waveform recorded in the same subjects on various occasions (Dustman and Beck, 1963; Kooi and Bagchi, 1964). It was proposed that the earlier waves of the flash VER are specific to the occipital region, whilst the later waves (>60 ms) diffuse over the whole scalp (Cobb and Morton, 1952; Ciganek, 1961; Gastaut et al. 1967). However, other workers (Kooi and Bagchi, 1964; Spehlmann, 1965; Rietveld et al. 1967) reported that the appearance of the early components was inconsistent and it was suggested that these, as well as other variations could be due to differences in the spatial arrangement of excited structures. Spehlmann (1965) felt that the "late wave" depended on visual input and therefore could be considered as being truly specific. In spite of these inter individual variations, Ciganek (1969), unlike Werre and Smith (1964) and Pampiglione (1967) felt that there is a standard human VER. It has been reported that the long latency or secondary components are altered by stimuli and psychophysical variables such as pattern, attention (Spehlmann, 1965; Perry and Childers, 1969; Regan, 1972; Wastell and Kleinman, 1980).

As previously mentioned, the VER is largely thought to represent central function. Many workers have shown that most of the VER amplitude is accounted for by the fovea with a rapid reduction in contribution occurring beyond 2^{o} from fixation, even more so for patterned stimuli (Copenhaver and Perry, 1964; Rietveld et al. 1967; Harter and While, 1968; Armington, 1968; DeVoe et al, 1968; Harter, 1970; Armington and Brigell, 1981). Copenhaver and Perry (1964) showed that the curve for the VER amplitude (using a 2.5^{o} spot) along the horizontal meridian approximated to the distribution of the retinal cones. Armington and Brigell (1981) found that with low level illumination, the VER decreased substantially to fine patterns in the central field as would be expected. They concluded that the VER was much more critically dependent than the ERG upon spatial frequency and retinal location. Riggs (1969) and Riggs and Sternheim (1969) also reported that the VER was much more sensitive to small wavelength changes to patterned stimuli than the ERG, once more reflecting the central nature of the VER. All of the above workers attempted to control light scatter in their experiments.

Other factors which enhance the contribution of the macular region (especially the fovea) towards the VER, are 1) the foveal projection in the striate cortex is located superficially at the occipital pole, therefore the occipital electrodes are nearer to this area and 2) the ratio of foveal to extrafoveal representation in the occipital cortex is increased by a factor of 1000 in comparison to the retina (Riggs and Wooten, 1972) which would indicate that the VER is mainly a function of central cone activity.

The latency of the peak of maximum positivity in the flash VER has been reported as occurring from 50 to 375 ms (Cobb, 1950; Ciganek, 1969, Kooi and Bagchi, 1961, 1964; Spehlman, 1965; Zerlin and Davis, 1967, Halliday 1976), however, in our laboratory, the most consistent and often largest component is seen between 100-130 ms, that is P_2 (Harding, 1974). It has been suggested that P_2 is a representation of the lambda wave which is a sharp Λ-like deflection of occipital origin seen in the EEG. They are triggered by voluntary eye movements in viewing a high contrast pattern rather than a diffuse light stimulus (Gastaut, 1951; Cobb and Pampiglione, 1952; Barlow, 1964). Gastaut et al. (1966) felt that the P_{2a}, part of the P_2 component (Figure 3.9) was associated with cone activity whilst P_{2c}, was associated with the activity of the peripheral rods because during dark adaptation and eye closure, P_{2a} decreased in amplitude and P_{2c} increased. Kooi and Bagchi (1964) in their topographical study on the flash VER found that the amplitude of the N_1P_1 component (using Harding's notation) was maximal over the parietal regions, N_2P_2 over the occipital regions and N_3P_3 over the central regions.

Since considerable interindividual variability was observed in the VERs to flash stimulation perhaps because 1) unlike other perceptual measures, they lack luminance thresholds and can be obtained at levels far below the psychophysical threshold, giving amplitudes which are similar to the above threshold stimulation (Van Der Tweel and Verduyn Lunel, 1965) and 2) the frequency content is so varied, then many workers guided their attention to pattern specific responses. This diversion to pattern stimulation took place even more so because of the knowledge that cells at the ganglion, lateral geniculate nucleus

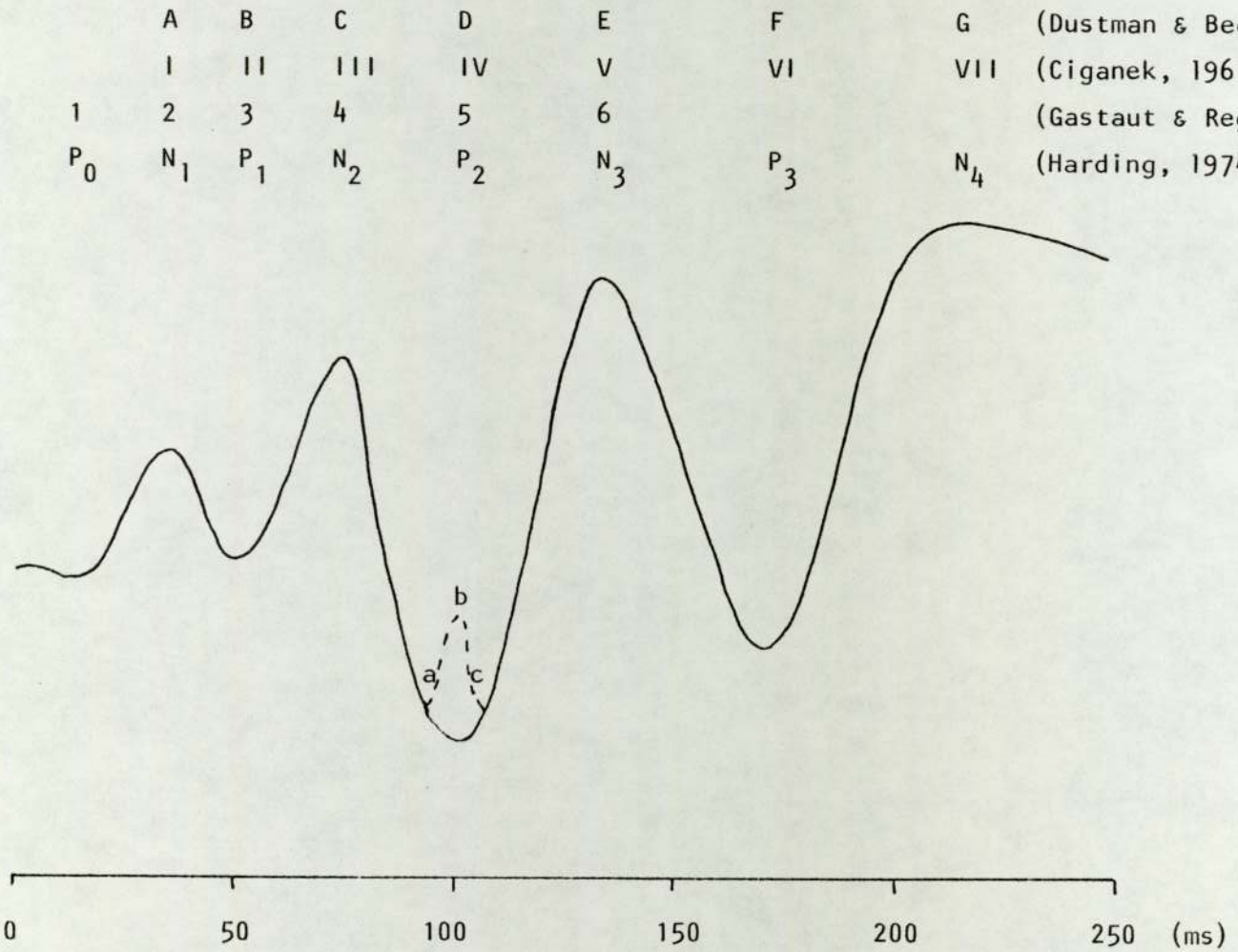


Figure 3.9 Morphology and nomenclature of normal VER to flash stimulation. The various forms of component labelling are shown above the waveform (after Harding, 1974).

and cortical levels demonstrated specific sensitivity to stimuli containing different edges, orientations, contours and wavelengths (Hubel and Wiesel, 1962; Gouras, 1969 ; Hubel, 1982 ; Kolata, 1982).

For the recording of pattern VERs, the earlier studies employed a stimulus pattern which was periodically back-illuminated by a flash of light. Although the findings in these experiments are meaningful there is a change in the mean luminance (Spehlmann, 1965; Rietveld et al. 1967; Harter and White, 1968, 1970; Harter, 1970). In order to try and maintain the total luminance flux constant with time, Spekreijse (1966) adopted the bar pattern reversal stimulus which was introduced by Riggs et al. (1964) to control the effect of stray light in ERGs. A chessboard pattern was used instead of the bar pattern to approximate more to the alleged circular shape of retinal receptive fields. It was postulated that if the ganglion cell discharge was determined by algebraically summing the reaction to patches of light or dark falling within a receptive field then the response to pattern reversal stimulation could not be larger than that to homogeneous field stimulation. It was found that with this pattern, not only was the response larger than with homogeneous stimulation but also that the VERs were responding to a change in spatial contrast whether this change was achieved by an increase or decrease of mean luminance level (Figure 3.10 a and b). This was unlike the simultaneously recorded ERGs which responded to net luminance change (Spekreijse et al. 1973; Reimslag et al. 1982). However, it was pointed out that the responses to pattern reversal stimulation may contain a luminance contribution because of the luminance modulation of the separate spatial elements. Nevertheless

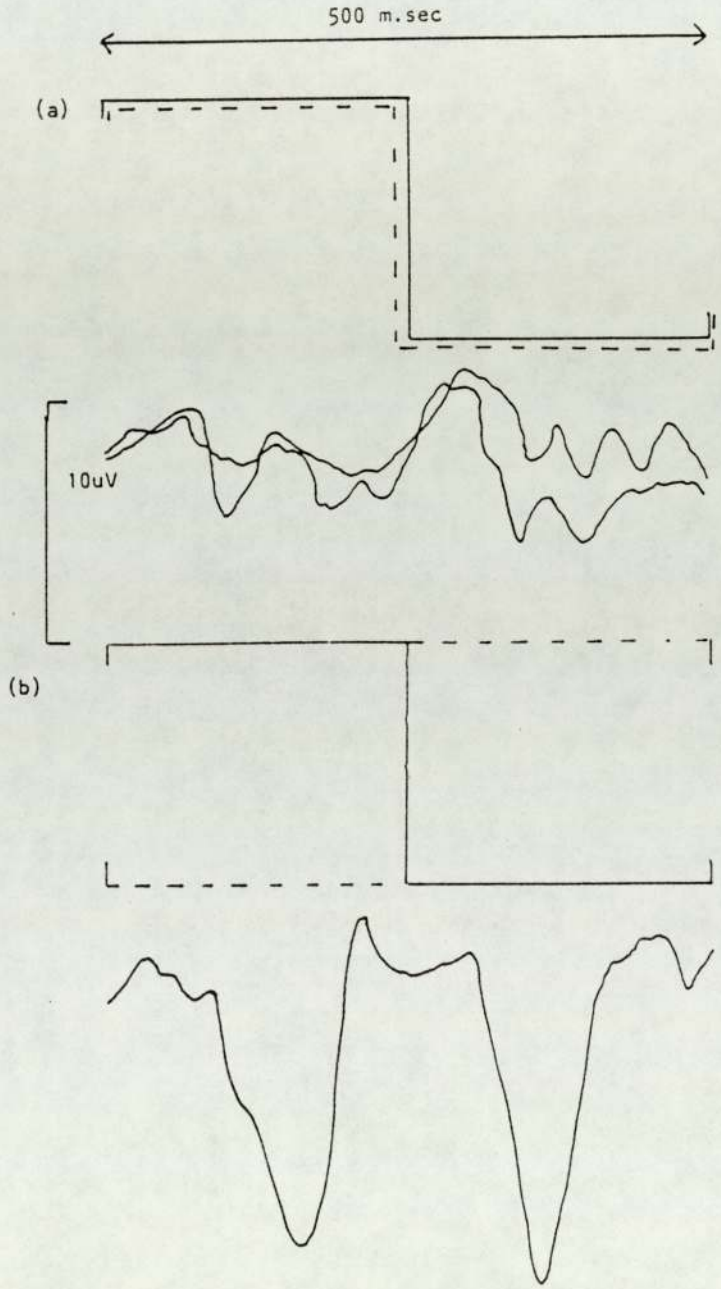


Figure 3.10 The VERs to (a) in-phase (homogeneous field) and (b) counter-phase (pattern reversal) modulation of two sets of squares. If both responses had the same origin, then the size of the response in (b) should be equal or smaller than that of response (a). However, the reverse is the case, which indicates that the two responses originate from different systems. (check size 15'; field size 6°)

(After Spekreijse et al. 1973)

there are many indications that these VERs behave differently and provide much more information about spatial contrast than those to unstructured stimuli. The pattern reversal VERs demonstrate less inter-individual variability (Van de Tweel, 1979; Halliday and Mushin, 1980); they are susceptible to defocussing of the pattern (Regan and Richards, 1973, Van Lith et al. 1977); like other pattern responses they respond maximally to certain check sizes for a given field size (Ristanovic and Hadjukovic, 1981).and they respond differently in demyelinating diseases, even after the recovery of visual acuity in retrobulbar neuritis due to multiple sclerosis (Halliday, 1976). Many of these aspects will be dealt with in further detail. By using triangular waves which lacked the effect of motion, Spekreijse et al (1973) showed that motion was not necessary to evoke the response to spatial contrast in pattern reversal stimulation. Many workers have subsequently adopted pattern reversal stimulation for theoretical and clinical studies (Cobb, et al. 1968; Halliday and Michael, 1970; Spekreijse et al. 1973; Shagass et al. 1976, Harding et al. 1978).

Another form of pattern stimulation was introduced to change the spatial structure of the stimulus without a mean luminance change. This has come to be known as pattern appearance-disappearance or pattern onset-offset, (Jeffreys, 1971; Jeffreys and Axford, 1972a and b, Spekerijse and Estevez 1972; Spekreijse et al. 1973). It has been found that the VERs obtained to this form of stimulation are of completely different waveform to those obtained to pattern reversal stimulation (Figure 5.3). Whereas it has been accepted that there is one most consistent component in pattern reversal VERs, that is, a surface positive component occurring at about

100 ms, it has been proposed that there are three consistent components in pattern onset VERs namely, a surface positive component, C1, occurring at 65-80 ms, followed by a surface negative component, C11 (very often the largest), occurring at 90-110 ms, and another surface positive component at about 160 ms, C111. There is also a response to the offset of illumination called "the off response" which is surface positive and can be seen if the presentation time is greater than 100 ms (Spekreijse and Estevez, 1972).

Both pattern reversal and pattern onset-offset stimulation have been used for the transient recording of VERs, mostly employing checkerboard patterns as they have been shown to be effective in producing clear responses (Spekreijse et al. 1973; Van der Tweel, 1979; Ristanovic and Hadjukovic, 1981). Van der Tweel (1979) and Drasdo (1980) suggested that their effectiveness was due to the complexity of the checkerboard pattern, representing many spatial frequencies and orientations, therefore stimulating many cortical cells.

Estevez and Spekreijse (1974) recorded VERs as the stimulation gradually progressed from pattern onset-offset to pattern reversal, attaining the same contrast at the initial and final stages (Fig 3.11). It was observed that the pattern reversal response was similar in waveform and latency to the disappearance response. These workers suggested that the subjective impression of "disappearance" of high contrast resembles a reversal stimulus (that is, an after image), concluding that pattern reversal represented a

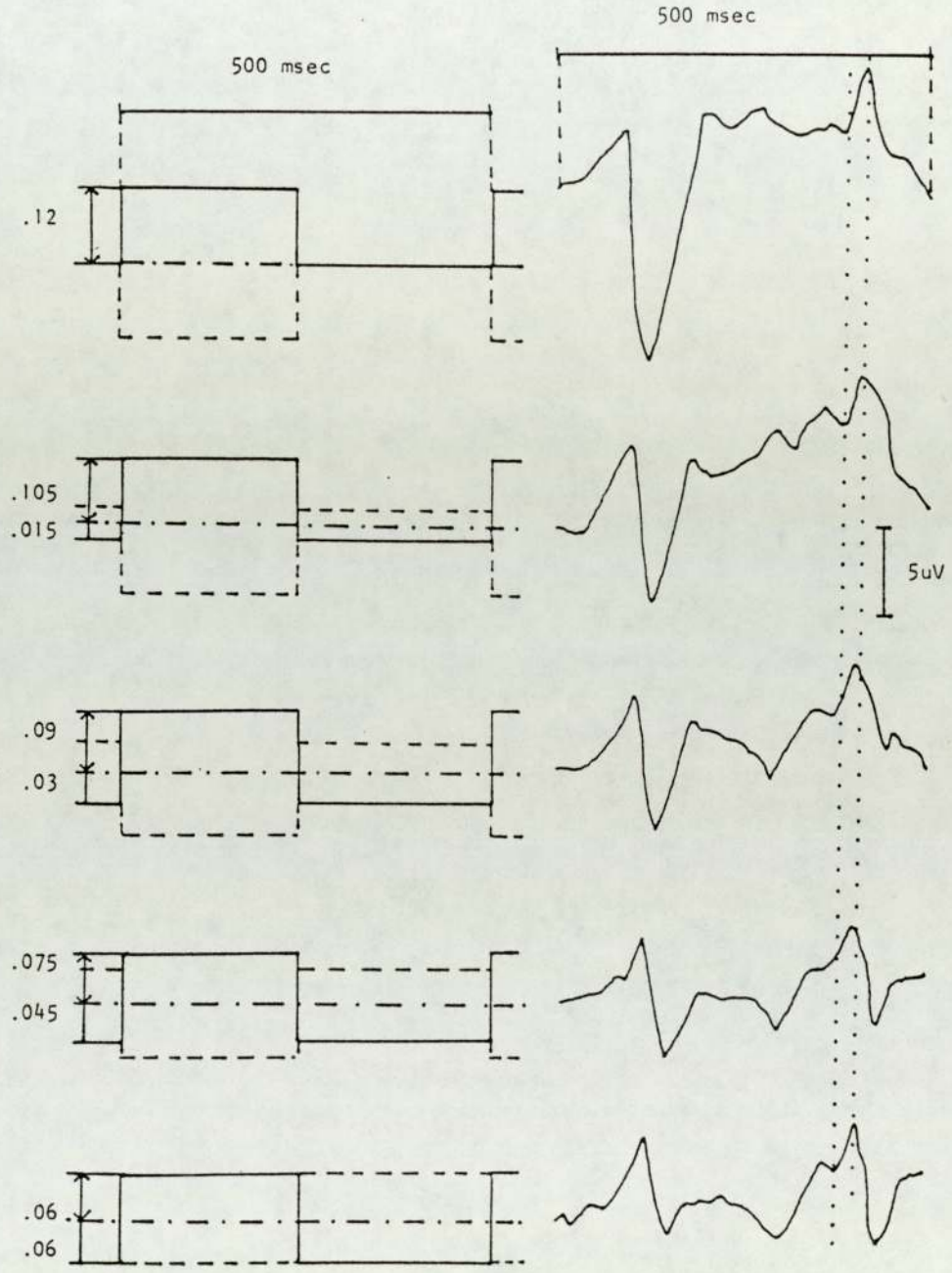


Figure 3.11 Transition of appearance-disappearance to reversal VERs. First column: schematic luminance time course of the two sets of checks; the luminance change of one set of checks is indicated by the continuous line; that of the other set by the broken line. First row: a pattern appears abruptly and after 250 msec is replaced by a homogeneous field; in the last row the pattern is reversed every 250 msec with the same contrast. Intermediate steps of asymmetrical reversal are shown in middle rows. Second column: evoked responses of a subject, corresponding to each stimulus.

(After Estevez and Spekreijse 1974)

complicated interaction between appearance and disappearance with a greater affinity to the latter. This view was supported by Kriss and Halliday (1980). In most of their studies, Spekreijse and his colleagues check sizes were 7'-20' and field sizes of 3^{o}-10^{o} with lower half field stimulation.

Topographical studies were performed on VERs to both forms of stimulation. Jeffreys (1971), Jeffreys and Axford 1972 (a and b), Jeffreys, (1977) carried out investigations to reveal the spatial distribution on the surface of the head of the components of the pattern onset response of short duration (to avoid adaptation) to different types of stimulation (that is, half-fields, quadrants, octants consisting of isolated solid or open squares etc of 14' check size and 6^{o} field). There were transverse and sagittal placements of the electrodes around the inion. These workers concluded that there is an additive relationship for the amplitude distributions of each component of different quadrant VERs, that is, the component distributions for a given half-field or full-field VER are the sum of those of the constituent quadrant VERs. They found that the peak latencies did not appear to vary much with either electrode position or different retinal locations used in their experiments, nevertheless the form and polarity of the amplitudes were dependent on retinal location. For a vertical distribution of electrodes, there was a reversal of the polarity of each of the three components in the VER to upper and lower halves of the visual field, generally being of smaller amplitude to upper half-field stimulation. For lower field stimulation, CI is positive, CII is negative and CIII is positive - except for this difference, the VERs

demonstrate similar types of changes to varying stimulus parameters for example, check size (Spekreijse et al 1973). Like Jeffreys and Axford (1972 a and b), Bartl et al (1978) described smaller responses for upper half field stimulation (in most of their subjects) to pattern reversal stimulation to relatively large check sizes (20' and 40') and field size. However, they observed that full field stimulation produced larger responses than half field and quadrant stimulation to various check sizes (also Onofrj et al. 1982).

For right and left half field stimulation and a horizontal distribution to pattern onset, Jeffreys and his co-workers (1971, 1972 a and b, 1977) obtained a prominent positive component (C1) on the contralateral side in most of their subjects, with this component reversing polarity near the midline and becoming smaller on the ipsilateral side (also Shagass et al. 1976). This is in contradiction to Kriss and Halliday's findings (1980) who found a positivity on both sides, being earlier and sharper on the ipsilateral side. The latter workers attributed this difference to varying electrode montages, including different reference points and the use of larger check and field sizes in their study therefore representing more paramacular activity.

The differences between upper and lower half fields and right and left half fields were also observed to pattern reversal stimulation by Halliday and his colleagues (Halliday and Michael, 1970; Michael and Halliday, 1971; Blumhardt et al. 1978, Kriss and Halliday, 1980). Michael and Halliday (1971) put forward a hypothesis for the reversal

of polarity of the prominent wave seen at about 100 ms for upper and lower half field stimulation. They used a midfrontal electrode and the two earlobes as reference points and found that the results to lower field responses remained relatively unchanged, but the upper field responses were significantly altered by changing the reference points. Although neither of these references was indifferent, it seemed as if the two earlobes tended to pick up upper field responses. Lehtonen and Koivikko (1971) also found that there was an ample response at the earlobe reference point and they suggested that a non-encephalic reference should be used, for example the chin. Nevertheless, they pointed out that the latter type of reference is more susceptible to technical disturbances and artefact, such as muscle activity. Like Jeffreys and his co-workers, Parker et al. (1982) opted for the earlobe reference in preference to the vertex as they claimed that the latter reference site resulted in distortion in the onset-offset responses. On the other hand, Van Lith, et al. (1980) and Crevits et al (1982) found no consistent difference between the morphology of the responses with either of these reference sites (that is, the midfrontal site and the earlobe) for pattern reversal and onset-offset stimulation, using whole fields and right and left hemi-fields.

By using dipoles, Michael and Halliday (1971) postulated that the upper field responses, arise from inverted neurones on the under-surface of the occipital lobe whereas the lower field responses arise from the neurones on the upper convexity. They concluded that the prominent component did not originate in the calcarine fissure but most likely from the extrastriate areas.

The type of VERs obtained to right and left half fields to pattern reversal stimulation has already been mentioned in section 2.3 in that a major positivity (about 100 ms) is seen on the ipsilateral side whilst a PNP type of response is seen on the contralateral side (Blumhardt et al. 1978). Van Lith et al. (1980) and Crevits et al. (1982) used Halliday's midfrontal position and Jeffreys earlobe position as reference sites (no marked difference was observed in the responses from either reference point) and recorded pattern reversal and onset-offset responses to whole fields and right and left hemi-fields. They confirmed the findings of Halliday and his colleagues for pattern reversal stimulation (P100 being maximum on the ipsilateral hemisphere) and of Jeffreys and Axford to pattern onset-offset stimulation (CI being maximum on the contralateral hemisphere). In addition to this, these workers reported that CIII and the off-response behave differently to CI, in that they were maximum on the ipsilateral side. These workers postulated that CIII and the off-response originated from the same dipole as P100 (Halliday's dipole) and CI originated from a dipole perpendicular to it (Figure 3.12), therefore the differences in the results were not due to electrode positions. However, this model does not seem to explain the results of Kriss and Halliday (1980) whereby a sharper and earlier positivity was obtained on the ipsilateral side in comparison to the contralateral side to stimulus onset. Like Kriss and Halliday these workers used a relatively large check size (40') and field size (18^{o}).

From the analysis of their results, Jeffreys and Axford hypothesised that CI (P_1)* originated from the striate cortex around the calcarine

* P_1, N_1, P_2 are more recent forms of notation for CI, CII and CIII respectively.

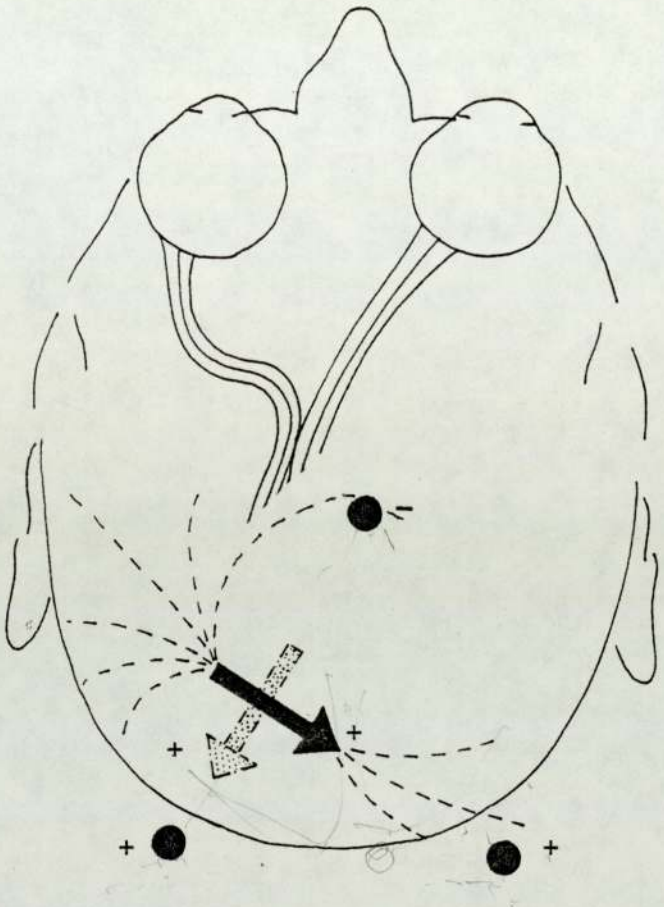


Figure 3.12

Dipoles in the left occipital lobes after right half field pattern stimulation. Black arrow : dipole of Halliday, probably also the origin of CIII of Jeffreys. Grey arrow: dipole, which may cause CI of Jeffreys (after Van Lith et al. 1980)

fissure and CII (N_1)* and CIII (P_2)* from the extrastriate cortex. However, Drasdo (1980 and 1982) and Lesevre and Joseph (1980) found that CI was maximal over the peristriate area in most cases for both luminance and colour contrast patterns (Drasdo claimed that it predominates on the right side). For smaller check sizes (3.5'), Drasdo (1980) reported that CII became largest over the striate cortex.

Various workers have shown that whereas CI responds mostly to luminance, CII is contour-specific but like CI, it has a dependency on contrast (Spekreijse and Estevez, 1972; Jeffreys and Axford, 1972a and b, Spekreijse et al. 1973; Jeffreys, 1977; Spekreijse, 1980). CIII has been found to be enhanced by high contrasts and binocular stimulation (Van der Tweel, 1979). Spekreijse et al. (1973) showed that the presence of 10% steady contrast was sufficient to half the amplitudes of the VERs to onset in comparison to starting with 0% contrast but having the same percentage increase. This was explained by saying that the higher the initial contrast, the smaller will be the response to an increase in contrast as it becomes saturated to pattern onset. They pointed out that steady contrast did not produce adaptation but the response to an increase in contrast depended on whether one started at a sub-threshold, threshold or super-threshold level. On the contrary, the off-response remained relatively unaffected to steady contrast which indicated that it was the actual step-down in contrast rather than the actual initial and final values which mattered. It was shown that the longer the time that the pattern had disappeared, then the larger would be the re-appearance response (Spekerijse et al. 1973, Spekreijse and Van der Tweel, (1974). Van der Tweel (1979) proposed that the "disappearance effect" of contrast fell exponentially

with time and it depended on what part of the curve the disappearance effect had reached before reappearance was once more initiated.

Spekreijse et al (1972), Van Der Tweel and Spekreijse (1973), Van Der Tweel and Auerbach (1977) and Van Der Tweel et al. (1979) found that the VERs of a rod monochromat and an achromat demonstrated all the components of a normal subject whilst that of an amblyopic eye lacked the contour sensitive CII. These investigators concluded that, although larger check sizes and higher contrasts are necessary for the monochromat and achromat, once the mechanism that generates the pattern response is triggered, the same response is obtained regardless of the nature of the signal that releases it.

Spekreijse et al. (1973) and Jeffreys (1977) showed that overall luminance change associated with the presentation of the pattern did not markedly alter the waveform of the pattern onset VERs in most subjects, suggesting that the response was chiefly affected by spatial contrast.

Jeffreys (1980) found that for the onset response for identical electrode positions on different subjects, there was a substantial variation in the relative amplitudes of the constituent peaks and in the peak latencies. Perhaps this would account for 1) the statement made by Van Der Tweel et al. (1979) that the responses appear always to contain CII with the other components being inconsistent in appearance and 2) the large variability obtained in Lesevre and Joseph (1980) in normals for onset and offset components. Jeffreys also showed the enhancement of the onset components for various electrode positions and stimulus types (for example, right or

upper hemi-field) and suggests that ideally, prior surface mapping investigations should be performed for each subject,(also Darcey et al. 1981). He claimed that the prominent positive peak seen in pattern reversal stimulation and the offset-response consists of two successive but temporally overlapping positive components and the composite peak depended not only on the latencies of the individual components but also on their relative amplitudes.

Although many of the physical factors affecting the flash and pattern VERs have already been mentioned a general list of the influencing factors will now be given.

3.2.3 Factors Influencing Flash and Pattern VERs

A. Conditions of Stimulation.

1. Type of Stimulation, that is flash or pattern.
2. Monocular and Binocular stimulation.
3. Factors pertaining to the stimulus, that is retinal location field and check size, contrast etc.
4. Frequency and duration of stimulus.

B. Physiological and Psychological Factors

1. State of adaptation
2. Pupil size
3. Refractive errors and accommodation
4. Habituation and attention
5. Interindividual and intraindividual changes
6. Habituation and other variables.

A. Conditions of Stimulation

1. Type of Stimulation

As already discussed, the morphology of the VER changes markedly depending on whether the stimulation is to flash, pattern reversal or pattern onset-offset. This would indicate that each type of stimulation represents various forms of cortical activity in the occipital areas. Harding et al. (1980), and Komsuoglu et al. (1981) suggested that the flash response represented activity in the cerebral cortex which was not as specific to the integrity of the visual pathway as the pattern reversal responses.

In his topological studies, Drasdo (1982) reported that whereas the pattern onset response is subject to many local variations, the pattern reversal is less so, and the flash response is very similar on all electrodes. It was previously mentioned that the checkerboard pattern is one of the best forms of stimulation for producing large and clear VERs, especially with isolated checks (Spekreijse et al. 1973; Jeffreys 1976, 1977). However, square and sine wave gratings are found to be useful in certain instances such as testing for orientation specific components and they are often used in the recording of steady-state VERs (Spekreijse, 1966; Millodot, 1977; Regan, 1977; Smith and Jeffreys, 1978; Brocklin et al. 1979; Armington and Brigell, 1981).

2. Monocular and Binocular Stimulation

For flash stimulation, Gouras et al (1964) reported that the ratio

of binocular to monocular amplitude could be as high as 100%. However, Perry et al. (1968) found this value to vary only from 8-43% depending on the electrode position. The difference in these results could be partly due to dissimilar stimulating conditions, for example, field size. Ciganek, (1970) observed that for high intensity (foveal cone response) and very low intensity (peripheral rod response) flashes, the increase in amplitude for binocular stimulation was 42% and 100% (or more) respectively. This was explained on the basis that the foveal cone signals project bilaterally to both hemispheres and converge on the same cortical neurones; however, with the peripheral rods, there is more unilateral transmission of signals, resulting in greater binocular addition.

For pattern reversal stimulation using a small check size (14'), Trick et al. (1982) found that the mean binocular amplitude exceeded the mean monocular amplitude by a factor of 1.4 which was in accordance with the psychophysical results, for example, visual acuity.

3 Factors Pertaining to Stimulation

a Retinal Location

The retinal location of a stimulus has already been shown to play an important role in the clarity and size of the VERs to flash stimulation (Copenhaver and Perry, 1964; Rietveld et al. 1965; Rietveld,1966). For pattern reversal stimulation, the responses to vertical and horizontal

half-fields demonstrated differences in polarity and maximal responses were seen over various areas of the occipital and surrounding cortex (Halliday and Michael, 1970 ; Michael and Halliday, 1971; Blumhardt et al. 1978; Kriss and Halliday, 1980). A similar type of behaviour was observed in the responses to pattern onset-offset stimulation (Jeffreys, 1971, 1976, 1977, 1980; Jeffreys and Axford, 1972 a and b; Kriss and Halliday, 1980).

There are other factors which are closely associated with the retinal location of a stimulus and they are:

1. Spatial frequency of grating or check size, and
2. Field size.

Rietveld et al. (1967) found that for flash-presented pattern to 20' checks, the peak in amplitude of the response was already reached for a field size of 2^{o} for two positive components (about 100 and 200 ms). Armington (1964), Harter and White (1968) and Armington and Brigell (1981) demonstrated that relatively small checks and higher spatial frequencies were best for foveal stimulation whereas larger checks and lower spatial frequencies were best for the more peripheral retina. At 12.5^{o} - 27.5^{o} from fixation, check size did not seem to influence the VER waveform (Harter and White, 1968). It was suggested that these results reflect the various sizes of retinal receptive fields. (Harter, 1970).

Eason et al (1970) showed that for flash-presented pattern, the optimum check size for stimulating the upper and lower hemifields

differed, being smaller for the upper field. They proposed that this was in accordance with the requirement to detect distant objects in the sky and near-by objects on the ground.

Similar to the findings of Harter and White (1968) and Harter (1970), Ristanovic and Hadjukovic (1981) and Meredith and Celesia (1982) observed that for pattern reversal stimulation the VERs were largest when small checks (7.5' - 3.0') were viewed for smaller field sizes ($<4^{o}$) whereas larger checks (30' - 60') were optimal for larger field sizes. Similar to Rietveld (1969), Harding and Crews, (1978) and Sokol et al. (1981), these workers reported that there was an increase in the latency for smaller check sizes.

For pattern onset-offset stimulation, a similar trend was taken for the optimum check size as was observed for patterned flash and pattern reversal stimulation. (Spekreijse et al. 1973). Like Harter (1971), Spekreijse et al. (1973) observed that the offset response was better stimulated by smaller checks. With a decrease in field size from 6^{o} to 1^{o}, Spekreijse (1980) noticed that there was a marked delay in latency and a broadening of the onset response and a decrease in amplitude. This result was surprising to this worker, as it would be expected that the central 1^{o} would greatly contribute to the larger field. This indicated that the response was not simply the sum of responses from parallel channels. This would agree with Armington and Brigell (1981) that the more peripheral retina makes some contribution to the VER.

b. Orientation and Size Specificity and Adaptation of the VER

From the findings of different workers that there are orientation specific cells in the visual system (see Section 3.2.1), it is not surprising that certain components of the pattern VER exhibit this specificity. Mecacci and Spinelli (1976) observed that the VER amplitude was not affected by pre-exposure to a sinusoidal grating differing in spatial ~~frequency~~ orientation by more than 1 octave (20^{o}). Kulikowski (1977) showed that the reversal VERs for low to medium spatial frequencies were not markedly affected by pre-adaption to a similar stimulus, however there was a significant decrease in amplitude of the response to onset-offset (also Smith and Jeffreys, 1978).

Jeffreys (1977) reported that short pre-exposure periods produced marked attenuation of CII and CIII but not of CI in pattern onset offset, even for low contrast patterns. This attenuation was enhanced by long pattern durations and short interstimulus intervals. Barber and Galloway (1979, 1982) observed the adaptation characteristics of the onset response, finding that CI hardly adapted and CIII adapted much more slowly than CII. The amplitude of CII fell exponentially with time, with the equilibrium value being reached after about five averages. This value was shown to depend much more on the inter-stimulus interval than upon the stimulus duration (the longer the inter-stimulus interval, the larger the equilibrium amplitude).

c. Contrast

Like psychophysical functions, Spekreijse et al (1973) found that pattern VERs to onset-offset demonstrate contrast thresholds which are dependent on luminance, that is, the higher the mean luminance the lower the contrast threshold. They also reported that the contrast at which saturation occurs, is lower, the higher luminance and larger the check size. As already stated the presence of steady contrast or even steady outlines within a pattern of squares, reduces the onset response but not the offset response (Spekreijse et al. 1973; Jeffreys, 1977).

Van Der Tweel et al (1979) reported that if the stimulus contrast at each adaptational level is a constant multiple of the threshold contrast, then the amplitude and shape of the response remains virtually consistent but there is a latency increase with decreasing adaptational levels.

d. Intensity of Stimulus and External Illumination

It has been found that an increase in the intensity of the flash stimulus is usually accompanied by a VER of greater complexity, larger amplitude and shorter latencies (Armington, 1964; Shipley et al. 1966). However, extremely intense stimulation can produce a reduction in amplitude (Perry and Childers, 1969).

The effect of external illumination also influences the VER. If there is a small percentage change in brightness, then the amplitude

of the VER would be small as compared to a large percentage change (Regan, 1972). Nevertheless, if very high percentage changes are used, then swamping of certain components occurs due to saturation (Van Der Tweel and Verduyn Lunel, 1965; Spekreijse, 1966).

For pattern reversal stimulation at high contrast levels, Halliday (1977) reported an increase of 15 ms per log unit in the P100 component over a 4 log unit change in mean luminance from scotopic to photopic conditions.

For pattern onset-offset stimulation, Van Der Tweel et al. (1979) and Spekreijse (1980) reported that a reduction of the mean luminance level resulted mainly in an increase of the peak latency of CII, of about 30 ms per log unit for 6 log units on passing from scotopic to photopic conditions at contrast levels which were fixed multiples of the threshold contrast at each luminance level.

e. Colour of Stimulation

As pattern colour stimulation has been included in the project, this topic will be discussed in a separate section (3.2.4).

4. Frequency and Duration of Stimulus

The recording of transient VERs usually entails stimulation at relatively low frequency (<4Hz) in order for the response to develop fully before the onset of another stimulus. According to Regan (1977a),

for transient VERs, the system is given a "kick" and its return to the state of rest is recorded. This "kick" may be a light flash or otherwise. On the otherhand, for steady-state VERs which employ higher frequencies, the system is gently shaken at a fixed repetition frequency and then wait until it settles down to a given response, such that any response cycle is like any other.

For flash stimulation a photic stimulator is used which produces a flash of extremely short duration (about 10 μs) and does not interfere with the response. Van der Tweel (1979) demonstrated that if the stimulation period in pattern reversal and onset-offset become sufficiently short, a sine-wave like response ensued.

The effect of stimulus duration and interstimulus interval in pattern onset-offset stimulation has been previously presented.

B. Physiological and Psychophysical Factors

1. Refractive Error

Copenhaver and Perry (1964) showed that by stimulating affected eyes with some form of neural lesion, the VER to flash (2.5^{o} spot) was reduced in the affected eye in comparison to the good eye. However, in stimulating eyes with refractive errors, this difference in amplitude was not seen.

Sphelmann (1965) noticed that with a +10D lens in front of a patterned stimulus, the response resembled that of diffuse stimulation. Harter

(1968) defocussed the checkerboard stimulus by using a graded series of lenses (+6D to -6D) and found that the amplitudes of two prominent components varied differently. He estimated the objective spherical refractions of two subjects using these components. Van Lith et al. (1976) used defocussing lenses on pattern reversal and flashed-pattern stimuli of various check sizes and concluded that the influence of defocussing was less for larger check sizes and higher contrasts. Other workers have employed steady-state pattern reversal VERs to assess the objective spherical and astigmatic refraction (Ludlam and Meyers, 1972; Millodot, 1977; Regan, 1977; Chiba et al 1979; Stadler and Muller, 1982) whilst Brocklin et al. (1979) assessed refraction by using both transient and steady state pattern reversal VERs and concluded that the transient method was more accurate for this purpose. In non-cycloplegic refractions, Duffy and Rengstorff (1971) and Brocklin et al (1979) reported that the largest responses were obtained at dioptric values more minus than the habitual refraction. Brocklin et al. suggested that it could be due to stimulation of accommodation by the negative lenses or due to the fact that subjects said that "they had to work harder" to maintain clarity with minus lenses, therefore artifactually increasing the VER amplitude. The former proposition would be contrary to the finding of Cornetta et al (1981) who measured an average decrease of 1 uV and an increase in implicit time of 1.5 ms per dioptre of increasing accommodation induced by minus lenses. Brocklin et al (1979) and Collins et al (1979) also found that the latencies of the most prominent positive components were delayed, accompanied by a reduction in amplitude with increased refractive error.

Howe et al. (1981) assessed the VA of subjects by employing pattern onset-offset stimulation. They first determined the contrast thresholds for various check sizes and then plotted a graph of contrast threshold versus check size. They estimated at which check size, a value of 100% contrast threshold was needed (as smaller check required higher thresholds). Their values correlated well with the Snellen acuity.

Regan (1978) pointed out that there are limitations in using the patterned VER as an assessment of VA as the optimal check size depends on frequency of stimulation. He also commented that smaller check sizes (<40') should be used as VERs to large checks, resemble those of flicker stimulation.

2. Age

Dustman and Beck (1969) and Dustman et al. (1977) investigated the effects of maturation and ageing in the flash VER in patients ranging from 1 month to 81 years old. Up to 6 years old, there was a rapid increase in amplitude with a decline thereafter until 14 years old when an abrupt increase appeared which seemed to stabilise at 16 years old. Like Kooi and Bagchi (1964), these workers found that with older subjects (about 67 years), the components before 100 ms were consistently larger and arrived significantly later. Unlike the above workers, Copenhaver and Perry (1964) reported a decrease in amplitude with increasing age.

Cosi et al. (1982) found an increase in all the components for the flash VER in elderly patients ($\bar{x}$ = 59 years) but more so in the earlier ones. They also felt that the increase of latencies were more evident than previously reported. It would seem that the discrepancies in these results could be partly explained by differing experimental conditions, for example, flash intensity.

For pattern reversal stimulation, Celesia and Daly (1977)) found that there was a significant increase in latency with age (using 15' checks), however, the amplitude did not markedly vary. They postulated that the delay in latency indicated a slowing of conduction in the visual pathways. On the otherhand, Shaw and Cant (1980) examining a similar age group (6 - 87 years old) but using 50' checks and larger field size, found that there was a wide variance in amplitude, being greatest in childhood and then declining until the fourth decade, when it increased again and after the sixth decade, it decreased. Snyder et al. (1981) also observed that the amplitude was greatest in childhood but after a mean age of 7 years, no significant age-related changes occurred (subjects varied from 4 - 90 years old).

Allison et al. (1979) reported a gradual decrease in latency from 10 - 50 years old, followed by a progressive increase thereafter. Stockard et al. (1979) found that there was no significant age effect from 20 - 55 years (for 32' checks), with an increase in variance (5 ms) for the over 50 age group and an increase in mean latency and variance in the over-60 group (no data was presented for this group).

Sokol et al. (1981) used two check sizes (48' and 12') and found that there was a decay in latency with increasing age for both check sizes, nevertheless, the rate of increase was nearly twice as fast for the smaller check which they believed to be due to the differential change in the capacity of the visual system to process spatial frequency information. These workers claimed that the decrease of pupil size with age only made a small contribution to the latency delay. No mention was made of amplitude changes. On analysing latency and amplitude changes in relation to sex differences for pattern reversal stimulation (50' checks), Halliday et al. (1982) found that there was a significant increase in latency with age in females (almost entirely between 50 - 70 years old) but not in males. There was no marked difference in amplitude with age for either sex.

3. Pupil Size

Perry and Childers (1969) stated that the effect of pupil size depended upon the stimulation conditions. With a smaller stimulus presented without a surround light or with essentially a full field surround light, there is a direct positive correlation between VER size and pupil size. However if a small stimulus is surrounded by a relatively small field ($<20^{o}$), then the pupil size is unrelated to the VER size.

Van Lith et al. (1978) reported that the relative difference in retinal illumination between a pupil diameter of 2 and 8 mm amounts

to more than 1 log unit for high contrast pattern reversal stimulation. Penne and Fonda (1981) observed the change in latency of P100 (using 75' checks) at several pupil diameters. He found that the mean latency increased by about 17.8 ms passing from a diameter of 8 mm to 1.5 mm using diaphragms and pharmacological miosis. The delay became much more evident on contracting from 8 to 2.5 mm than from 8 to 4 mm (3.6 ms). Hawkes and Stow (1981) ascribed these changes to the quantity of light entering the eye and not the slight reduction in VA caused by mydriatics or miotics.

4. Habituation and Other Effect Variables

Walter (1964) found that the amplitudes of VERs recorded from the human primary visual cortex were determined only by the stimulus parameters, but those outside this area were influenced by psychological factors such as attention However, there has been disagreement as to whether peripheral mechanisms play a role in habituation of the VER. Garcia-Ausst (1963), Perry and Childers (1969), Wastell and Kleinman (1980) claimed that variations in pupillary diameter were not of much significance in producing habituation whereas Bergamini and his colleagues attributed habituation solely to pupillary changes (Bergamini et al. 1966; Bergamini and Bergamasco, 1967). However, Regan (1972) casts some doubts on this, especially since at high brightness, the amplitudes are little affected by changes in stimulus intensity.

Perry and Childers (1969) observed that habituation was more likely to occur in trained subjects. These workers believed that if precautions are taken during recording (for example, a pause between each viewing) and instructions are given to the patient (for example

to maintain fixation during viewing), then the effects of habituation and other variables such as loss of attention are reduced. Ciganek (1967) found that the amplitudes with attention were significantly greater than those with distraction. In the case of pattern stimuli, the act of defocussing the elements as well as inaccurate fixation pose problems leading to alterations in the latency, and amplitude of the VER (Uren et al. 1979; Galloway, 1981).

5. Intraindividual and Interindividual Variability.

The variability of each VER has been lessened by increasing the number of sweeps but on the otherhand, too many sweeps enhance the influence of psychological variables, for example, fatigue.

Dustman and Beck (1963), Jacobson et al (1968), Perry and Childers (1969) and Galloway (1981) reported that the variability of the VERs from a given subject over a period of time is small.

Aunon and Cantor (1977) recorded the flash VERs of one subject at single sessions in 5 laboratories with different instrumentation (having equivalent settings). The results were compared with VERs obtained at 8 weekly sessions at one of the laboratories. The interlaboratory standard deviation was over twice as large as the intralaboratory standard deviation measured over an 8 week period. This result was attributed partly to different interlaboratory equipment. Intrasession variation was significantly less than intersession variability, however this was mostly amplitude variability.

Many other workers have also stated that the variability of amplitude is greater than that of latency in flash and pattern stimulation (Zerlin and Davis, 1967; DeVoe et al. 1968; Ciganek, 1969; Perry and Childers, 1969; Regan, 1978; Brocklin et al 1979). On recording the flash VERs in children from 6 - 15 years, Callaway and Halliday (1973) found that the reasonably high variability in amplitude decreased with increasing age, possibly because of better attention.

For pattern reversal stimulation Stockard, et al. (1979) retested 15 subjects at an interval of 3-9 months after the original study and found no significant intersession variability of the P100 component.

6. Sex

Perry and Childers (1969) said that it was not fully confirmed that females demonstrated shorter latencies and higher amplitudes than males. Dustman et al. (1977) reported that during childhood, the VERs of males were larger than those of females but the situation reversed during adolescence and adulthood.

For pattern reversal stimulation, Stockard et al (1979) reported that females had slightly but significantly shorter latencies than males.

Snyder et al (1981) found that females in the younger age group (6-20 years) had signficantly larger amplitudes than age-matched males whilst no marked difference was observed for the older group (21-59 years). They also reported that in a comparison of amplitudes between younger and older females, the younger group demonstrated

significantly larger reponses then those of the older group. This was not seen for the male group. Halliday et al. (1982) reported that females demonstrated markedly larger amplitudes than males throughout the 15 - 70 age range examined. There were also shorter mean latencies in females. It was suggested that these differences between the sexes could be related to smaller average head sizes and skull thickness and also higher deep body temperature in females.

3.2.4 Colour, with Special Reference to Colour Checkerboard Stimuli.

The proposal made by Young (1802) that there are three receptor mechanisms in the retina responding maximally to red, green and blue, originated when Newton declared that colour was not a property of light itself. Helmholtz (1852) went on to postulate that there was an overlapping of the sensitivity of the three mechanisms so that appreciation of all colours and hues could be obtained. This is now called the Young-Helmholtz theory of trichromacy. There has been experimental evidence for this theory from microspectrophotometric investigations (Marks et al. 1964; Brown and Wald, 1974; Bowmaker et al. 1980), histochemical investigations (Marc and Sperling, 1977) and threshold measurements (Stiles, 1959).

The microspectrophotometric studies (which involve obtaining absorption spectra of individual cones) revealed that the cones of humans and monkeys fall into three main classes, having maximum

absorptions in blue (440 nm), green (540 nm) and red (570 nm) with considerable overlap of the three curves. Marc and Sperling (1977) identified histochemically in primates, a much smaller number of blue cones (<10%) in comparison to red and green cones. This was supported by Van Norren and Padmos (1973) and Mehaffey and Brown (1974) who found that the blue cones only made a small contribution to the cone ERG. Van Norren and Padmos also observed that the "blue" cones were distributed in a regular manner and slightly peripheral to the red and green cones which were randomly distributed. In addition to this, the blue cones have comparatively large receptive fields and greater spatial summation which must underlie the lower VA. (Brindley ,1970). This was confirmed by the electrophysiological studies of Estevez et al. (1975) and Klingaman and Moskowitz-Cork (1979) whereby a larger check size had to be used to stimulate the blue mechanism. Stiles (1959) who developed a technique of isolating individual cone classes by adapting the eye to an appropriate steady background, identified five mechanisms of which π_1 to π_3 corresponded to the blue cone system and π_4 and π_5 to the green and red cone systems respectively.

Hering (1879) devised a theory which would explain the psychological laws of colour sensations. For example, according to the Young-Helmholtz theory, yellow is the combined response of red and green, however it is not perceived as "greenish red" like the greenish blue obtained by simultaneous excitations of green and blue cones. To deal with these difficulties, Hering assumed six distinct sensations arranged in three opposing pairs, white-black, yellow-blue and red-green which tend to

cancel each other out chromatically, that is red and green, and blue and yellow becoming white eventually. Evidence to support this theory comes from the electrophysiological studies which have revealed colour opponent cells starting from the ganglion cell level (Gouras 1972; De Monasterio, 1978), proceeding to the lateral geniculate body (Wiesel and Hubel, 1966) and the visual cortex (Dow and Gouras, 1973). Ingling (1977) reported that the spectral sensitivity of the colour opponent channels changes when progressing from dark to light adapted conditions which seems to cause a change in cone inputs.

From the experimental evidence, the two colour theories describe processes which operate at different levels of the visual system. This lead some workers to suggest "zone" theories in order to present the ideas of the two theories together (Figure 3.13).

In their review on colour vision from a neurophysiological aspect, Gouras and Zrenner (1981) summarised the process of analysing a colour image in the tonic retinogeniculate system through five distinct and parallel neural channels, three of which show strong colour opponent interactions. The strongly cone opponent (on-centre cells) are excited either by:- 1) red (that is, centre is "on" to red with strong inhibitions to green whilst the periphery is "on" to green and "off" to red); or 2) green (the converse of 1); or 3) blue (centre is "on" to blue with strong midspectral cone inhibition). This is the only strongly opponent channel which is also excited significantly by white light, although to a much less extent than the blue light regardless of its brightness.

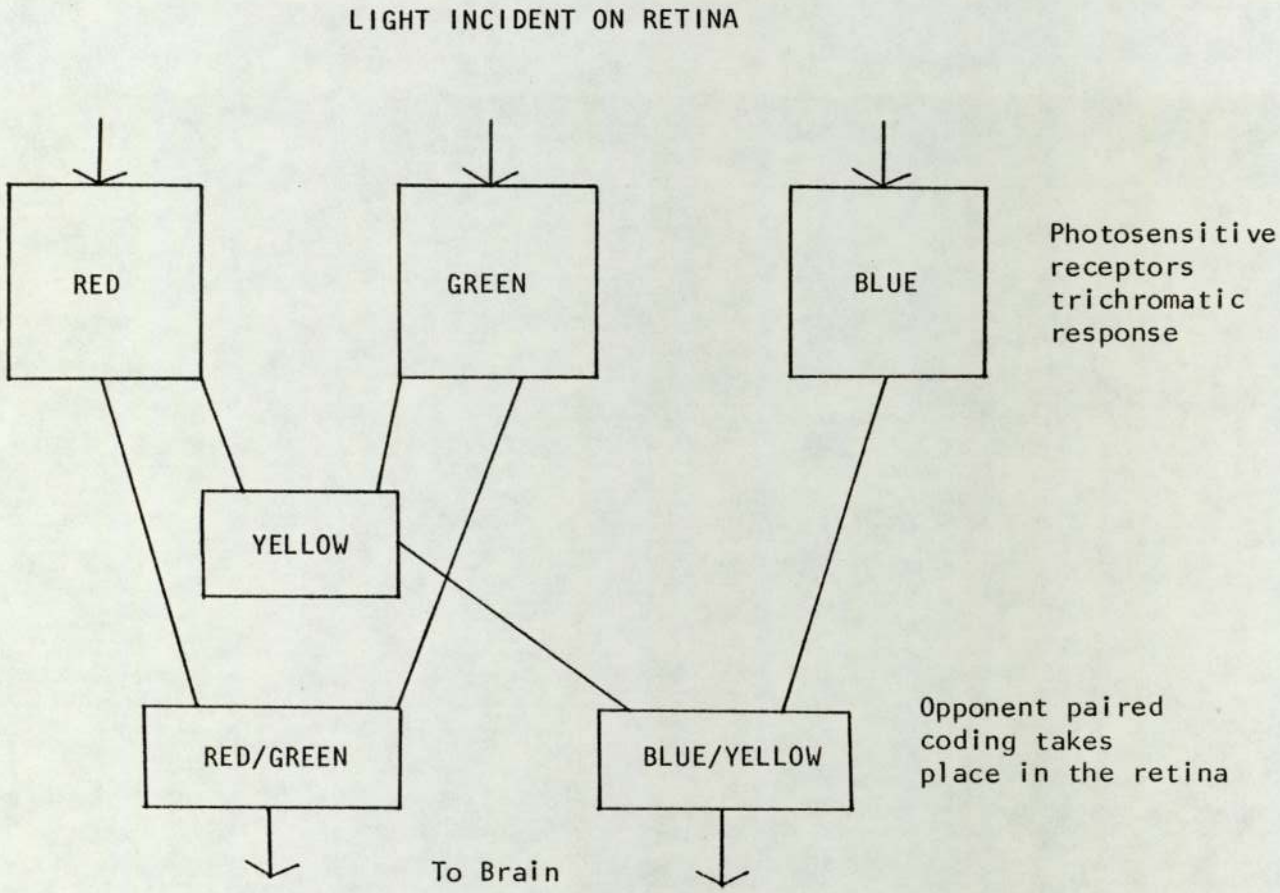


Figure 3.13

Diagram illustrating the zone theory of colour vision (after Voke, 1981)

There are many more red-green opponent cells, than blue opponent cells. However, only a small fraction of the total cells demonstrate such strong opponency. The other neural channels consist of:-

4) midspectral "on-centre" tonic cells, showing weaker or no colour opponency, responding at varying degrees to all colours (depending on the strength of colour opponency) but least to blue and black forms,

5) midspectral "off-centre" cells which tend to be inhibited by all light unless there is sufficient brightness in the surround or if a darker form (especially blue or black) moves into the centre.

In the striate cortex, spatial colour and brightness detectors are constructed from the retinogeniculate input since contrast gradients rather than local intensities appear to be the elements in images that maximally activate the cortical cells. Spatial colour contrast detectors respond best when the colour contrast across a contour gradient is maximal and for this reason the strongly colour opponent geniculate cells have been proposed to perform this function. The weaker opponent cells are used for luminance contrast and for the so-called "yellow" channel. It has been postulated that the three major variables of colour vision, brightness, hue and saturation are sensed separately by each detector (that is, separate luminance, red-green, blue-yellow and white-black contrast detectors).

Colour Defects

Rushton (1975) demonstrated that the deficiencies of congenital colour defectives are at the retinal level, either lacking one of

the colour pigments or having an anomalous pigment in one type of cone. The classification of congenital colour defects is beyond the scope of this thesis, (see Pokorny, et al 1980).

Acquired colour defects are known to be more variable than congenital ones (Pokorny, et al 1980). Verriest (1963) classified the acquired colour defects based primarily on the axis of major chromatic discrimination loss (Table 3.2). They are as follows:-

1) Type I, red-green defect - The chromatic discrimination on the red-green axis progressively deteriorates with a parallel loss in VA. Simulatenously, the photopic luminosity curve changes, finally leaving only a scotopic curve. This type of defect is seen in retinal disease primarily involving the photoreceptors of the posterior pole associated with a major loss in VA and eccentric fixation.

2) Type II red-green defect - the hue discrimination for the red-green axis progressively deteriorates with a concomitant milder blue-yellow loss. The relative luminous efficiency function remains approximately normal. Initially the colour discrimination is characterized by reduction in apparent saturation of most chromatic stimuli. In advanced stages, there is a neutral zone in which colours appear grey (about 500 nm). With severe loss in VA, the neutral zone widens to include the whole midspectral region. This defect is seen in optic nerve involvement such as retrobulbar neuritis, optic nerve intoxications. 3) Type III blue-yellow defect - This is characterized by loss of chromatic discrimination on the blue-yellow axis with a comparable deficit in VA. In the early stages, there is confusion in the "blue" region of the chromatacity chart with the

Name	Classification by Performance			Usual Visual Acuity	Usual Outcome
	Colour Matching	Discrimination Deficit			
		Major Axis	Severity		
Type I, acquired red-green	Trichromatic ↓ Monochromatic	Red-green	Mild ↓ Severe	Moderate to severe reduction	Achromatopsia (scotopic)
Type II, acquired red-green	Trichromatic ↓ Monochromatic	Red-green Concomitant (blue-yellow)	Mild ↓ Severe, mild	Moderate to severe reduction	May recover or progress to severe
Type III, acquired blue-yellow	Trichromatic ↓ Dichromatic (monochromatic rarely)	Blue-yellow	Mild ↓ Moderate	Mild to severe reduction	Various

Table 3.2

Classification of Acquired Colour Vision Defects based on the findings of Verriest (1963)

vision becoming dichromatic at a later stage. This defect occurs in a variety of diseases involving choroidal, retinal and neural disorders and hence cannot be ascribed to a specific lesion. Ageing also gives rise to blue-yellow defects caused mainly by discolouration of the lens as well as retinal changes.

Coloured checkerboard stimulation.

Regan and Sperling (1971); Regan (1972, 1977b); Regan and Spekreijse (1974) and Spekreijse and Van der Tweel (1974) devised a method of eliciting pattern specific chromatic VERs whereby they presented equiluminant alternate red and green checks, 1) in transient pattern appearance form, 2) steady state pattern reversal form and 3) transient pattern reversal form but this time the luminance of the red and green checks were modulated so that the instant when the red checks decreased in luminance, the green checks increased and vice versa (but not exchanging positions, Figure 3.14). These three types of stimulation were used on normal and deuteranopic subjects. From their pilot studies, they showed that the VERs are pattern specific and not artifacts of intensity changes, chromatic aberration or luminance contrast.

They found that with the first two types of stimulation , the normals demonstrated pattern specific responses whilst the deuteranope did not elicit any discernible responses. On the otherhand, the third type of stimulation produced responses only in the deuteranopes

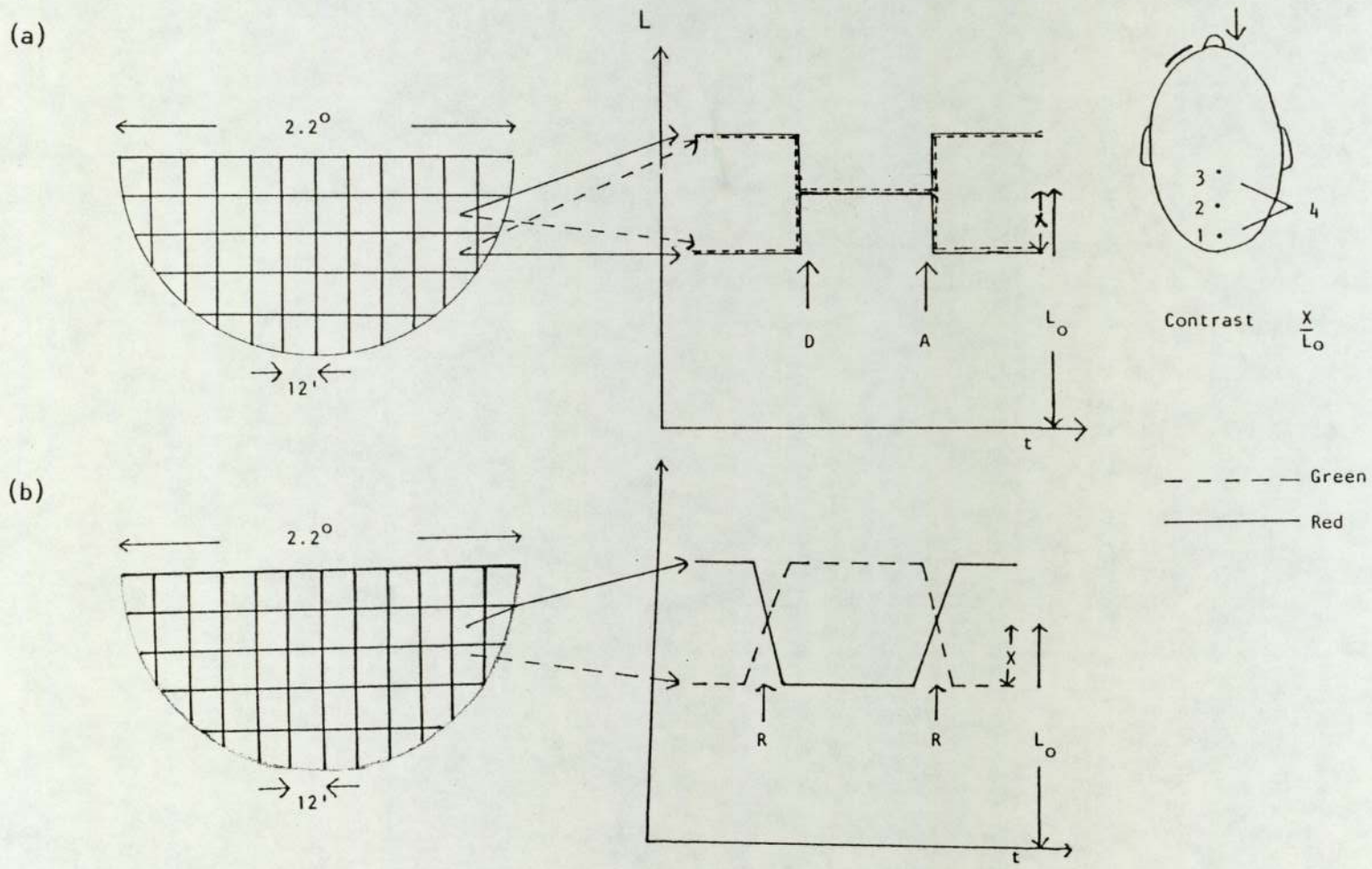


Figure 3.14
(a) The stimulus was the abrupt appearance of a pattern of red and green equiluminant checks from a previously unpatterned yellow field, that is, pattern appearance-disappearance (b) transient pattern reversal form but the luminance of the red and green checks were modulated so that at the instant when the red checks decreased in luminance the green checks increased and vice versa. Electrodes were placed (1) 1cm, (2) 5.5cm and (3) 10cm (above the inion along the midline, referred to the left mastoid) (After Reagan and Spekreijse, 1974).

(which they claimed were due to luminance changes) but not in the normals. They explained these results by saying that the mere presence of equiluminant squares (as in 3) was not sufficient to produce chromatic contrast VERs but there also had to be a change in chromatic contrast. They proposed a model for the colour coding of pattern VERs (Figure 3.15) whereby the red and green signals are still largely segregated on arriving at the first contrast sensitive stage. They felt that if the red and green signals were pooled prior to this first stage, then the equiluminant checks as in (3) would have produced a response in normals. The absence of responses could be predicted by their model whereby, the checks would "be seen" by say, the red channel as monochromatic with the neighbouring green checks appearing much dimmer, therefore the contrast between adjacent checks would never reverse, hence presenting steady contrast which saturates the system. However, if the luminance of the green checks was sufficiently increased, then there would be a response which was explained by the overlap of spectral sensitivities of the contrast sensitive colour channels.

These workers also observed that in the deuteranopes, the amplitudes of the VERs to pattern onset-offset and reversal stimulation (conditions 1 and 2) fell to a minimum when the checks were equiluminant but the normal responses did not demonstrate any such minimum, further showing that the normal VERs were produced to chromatic contrast and not to luminance changes. These results indicated to these workers that the colour defective was responding to the respective photometric luminances of red and green and also the signals from the colour channels were pooled before arriving at the first contrast sensitive

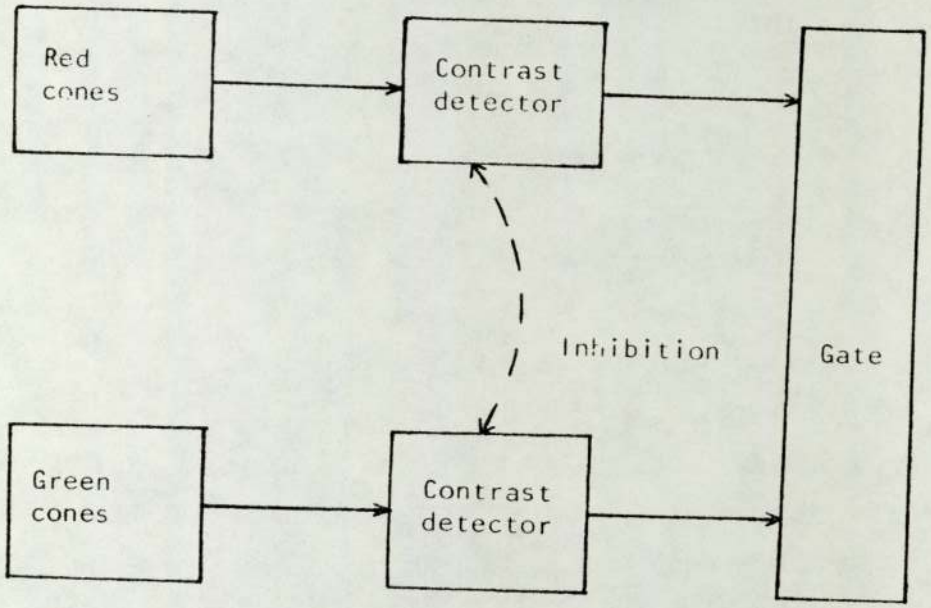


Figure 3.15

Pattern VER: simplified model of colour organisation.
(After Regan, 1977).

mechanism. They concluded that pattern specific stimuli were more useful in assessing colour defects than unstructured stimuli.

Dixon (1981) also found that with transient pattern reversal equi-luminant red-green stimulation (54' check), 7 colour defective subjects (with red-green agnosia) demonstrated responses of longer latency and reduced amplitudes in comparison to those of normals.

3.3 VISUAL FIELDS

3.3.1 Introduction to Visual Fields and Reasons for Choosing the Static Method of Campimetry.

The importance of the clinical investigation of the visual field was first propounded by von Graefe in 1856 who recorded the findings obtained by moving bright stimuli on a uniform background. This report was followed by the invention of a perimeter by Forster in 1868. Since that time, many types of visual field equipment have been developed which range from the conventional type of instrument (for example, Bjerrum screen) to the fully automated computerised instrument (for example, the Octopus). All these items of equipment have been designed so that they can be used either for static and/or the kinetic method of perimetric examination. The object of each method is to try and detect the minimum discernible luminance difference between the background (L) and target (ΔL), however, this is achieved by different means in the two methods. With the static method, the object is stationary but its luminance is varied at a fixed location whereas with the kinetic method, the position of the object is varied with fixed luminance although its size can be altered.

In order to explain the purpose of kinetic perimetry a concept developed by Traquair (1938) will be illustrated. This investigator likened the visual field to an "island of vision within a sea of blindness" and the visual field chart to a contour map (Figure 3.16). As the sensitivity of the retina gradually increases on passing from the periphery to the centre (see Section 3.1), it has been accounted for in kinetic

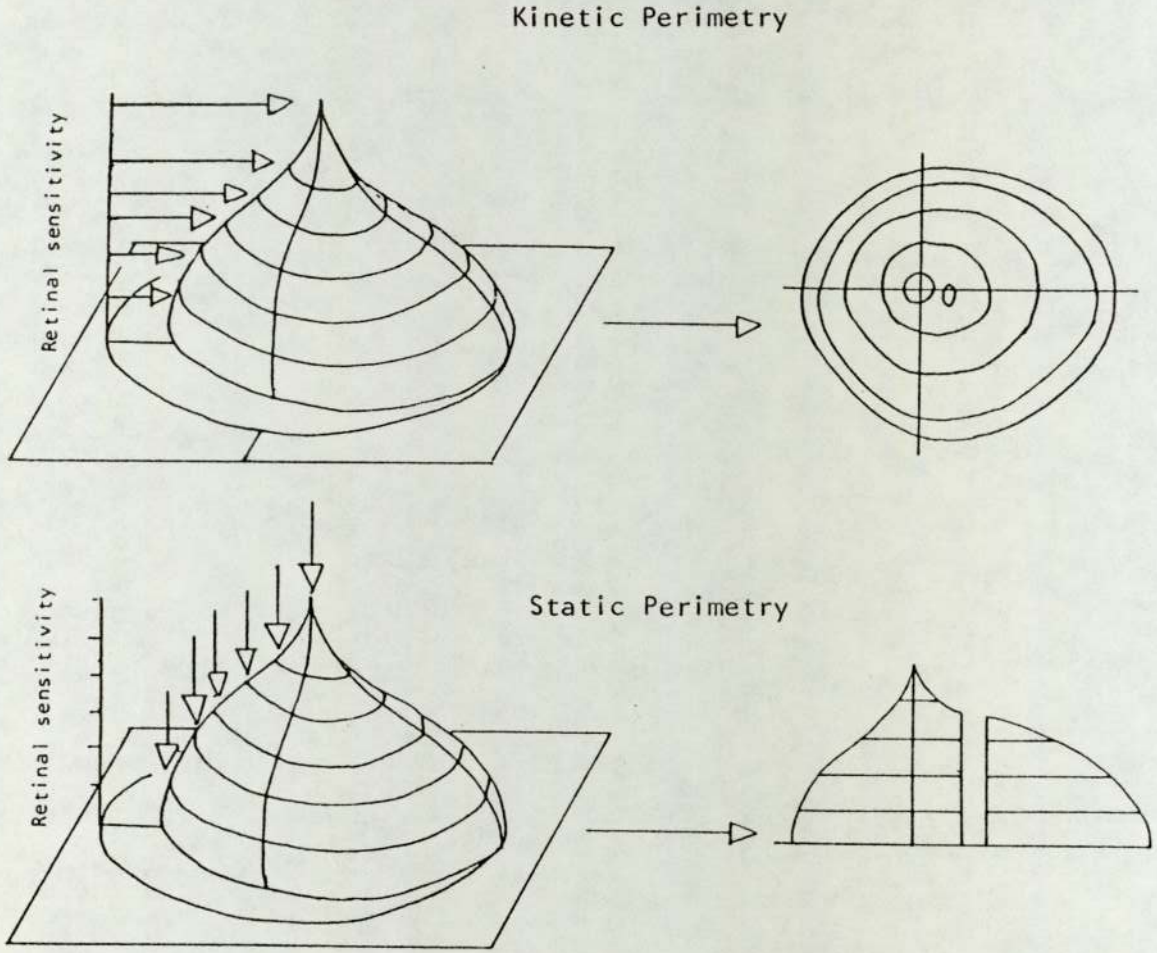


Figure 3.16 Two methods of measuring Traquairs "island of vision"
(Top) In conventional kinetic perimetry, a moving test spot of fixed contrast to the background approaches the island (arrows). Isopters, lines connecting all points of equal sensitivity to light, encircle the island. (Bottom) In static perimetry, the island is approached from above; a stationary test object measures elevation (sensitivity) at selected points by increasing in contrast until detected by the subject

(After Harms 1960)

perimetry by using ever-decreasing target sizes. Therefore the area within which each target is visible becomes smaller and smaller, so that a series of ever-diminishing circles is formed resembling contour lines. Each of these contour lines, known as an isopter, is obtained by moving a given target from a region of "non-seeing" to "seeing" along different meridians of the perimeter. Hence an isopter is a line of equal sensitivity to light contrast. It is expressed as a fraction of target size over the distance at which the test is performed, for example 3/330. The size of each isopter is also dependent on the colour of the target.

In contrast to kinetic perimetry, static perimetry approaches the plotting of the "island of vision" by measuring the sensitivity of the retina at selected points by decreasing the contrast (ΔL) at each point until it is detected by the subject. The difference between the two methods of measuring Traquair's "island of vision" is shown in Figure 3.16.

The function of a visual field examination is to reveal:- 1) the presence of visual loss at an early stage, 2) the position and shape of the field defect and 3) the density and size of the defect. Therefore the visual field has to be assessed along these guidelines and in order to be able to do this efficiently, the instrument which is to be used should satisfy certain conditions. However, prior to discussing the type of visual field instrument which has been chosen for this project, it is necessary to first consider the advantages and disadvantages of kinetic and static perimetry.

As mentioned in the previous paragraph, kinetic perimetry involves moving a target of fixed luminance along various meridians from a region of "non-seeing" to "seeing" and vice versa. In order to account for the gradient in retinal sensitivity, several target sizes (at least 3) have to be used.

On the otherhand, static perimetry involves the presentation of a stimulus at a fixed location within the visual field but its luminance is gradually changed from sub-luminal levels until the light (flash) can just be discerned. With this method, it is possible to plot different isopters of equal sensitivity at various luminance levels (Bedwell and Obstfeld, 1970; Bedwell, 1974).

From the above description, there are certain differences between the two methods which become apparent. One of these is that kinetic perimetry necessitates the movement of the target and as the target is brought continuously closer to the threshold level over various locations, spatial interaction (successive lateral summation) may occur between the positions (Greve, 1975; Verriest, 1979). This is related to the fact that the visual system is highly developed for the recognition of moving objects and therefore the kinetic threshold depends on the direction and speed of the object motion. The speed at which the target is moved, changes with each investigator leading to a variation in the size of the isopter. This variation is enhanced since the speed of the target is also partly governed by the patients reaction time. These problems are not encountered in static perimetry as the stimuli remain stationary.

There are other factors which influence the results of the visual field plot which are as follows:-

1) Size and Luminance of Stimulus

Sloan (1961) and Fankhauser and Enoch (1962) showed that the effect of blur disturbs the perimetric values similar to a true loss in retinal sensitivity. Sloan found that for small sized stimuli, this effect became significant within the central 20^{o} and therefore refractive corrections should be worn. If the stimulus is too small, then there are increased problems due to refractive errors, patients with sub-normal VA and the presence of small angioscotomata produced by the retinal vessels. On the contrary, too large a stimulus does not allow assessment of a deterioration of the summation effect, which is an important factor in pathological visual loss (Bedwell, 1967; 1972).

It is known that areal summation increases with increasing distance from the fovea (Sloan, 1961; Davson, 1981), hence resulting in a gradient in retinal sensitivity. For this reason, kinetic perimetry requires isopters for different sized stimuli, to be recorded whilst in static perimetry, this can be accounted for by simply having larger stimuli as the periphery is approached in order to maintain the stimuli at the same fixed relationship to the luminance threshold across the visual field.

2. Positions of the Stimuli

For the early detection of visual field defects, the stimuli have to be positioned at locations which are most likely to be affected by the more common pathological conditions. In addition to this, it also has

to be remembered that there are greater variations in certain areas of the visual field, such as there is greater variation with increasing eccentricity from the fovea and in the temporal field (Greve, 1972; Greve and Wijnans, 1973; Harrington, 1976). Nevertheless, these two aspects are reconcileable and it is possible to design a pattern of multiple apertures in the central field (30^{o}) where sufficiently consistent results are obtained. This form of presentation requires the static method. Greve (1972) reported that there was no marked difference in the threshold levels for single stimulus and multiple stimulus presentation up to 25^{o} eccentricity. By using multiple stimulus presentation, the test takes advantage of the phenomenon of "visual extinction" whereby any possible difference of threshold contrast between two stimuli is intensified if they are simultaneously exposed. If one should fall in an area where the sensory mechanism is depressed and the other in a normal area, then only the latter would be perceived. Greve, (1975, 1980) suggested an array of 120-150 stimuli within the central 30^{o} as being the optimum situation for the early detection of small defects of $3\text{-}5^{o}$. However, even with multiple stimulus exposure, the testing period would be fairly long with so many stimuli, therefore a compromise has to be made.

For examination of the peripheral field, kinetic perimetry is still necessary. However, many workers have reported that 90 to 95% of visual field defects manifest themselves within the central 30^{o} and although kinetic perimetry of the outer areas should not be abandoned it should be used selectively (Blum et al. 1959; Harrington, 1971; Greve, 1975; Bedwell, 1978; Berman, 1978; Ogawa and Suzuki, 1979).

3. Adaptation of the Eye

The sensitivity of the eye changes with the general adaptation level of light reflected from the background screen (Bedwell, 1967, 1972, 1974; Bedwell and Obstfeld, 1970). Most visual field examinations are performed under mesopic conditions in order to avoid undue periods of dark adaptation and also to stimulate the rods and cones more or less equally. This level of adaptation has been reported to be effective in visual field examination (Bedwell, 1967; Shinzato et al. 1977).

The effect of background luminance on a 7' test spot is illustrated in Figure 3.17. It can be seen that as the background luminance decreases, the static curve moves upwards with a physiologically central scotoma appearing under dark adapted conditions.

4. Duration of Stimulus

Since kinetic perimetry relies upon the patients recognition of the appearance or disappearance of the stimulus, then the target is present for long periods during which time the patient is expected to maintain fixation. Not only does this become quite a difficult task for many patients, especially the elderly, but also patients tend to make small eye movements towards the stimulus since they know from which direction it will appear.

Henson (1980) also points out that the relatively long time interval which lapses between the instruction given to the patient and the occurrence of the actual event influences the probability of detection that is, it falls quickly within the first few seconds.

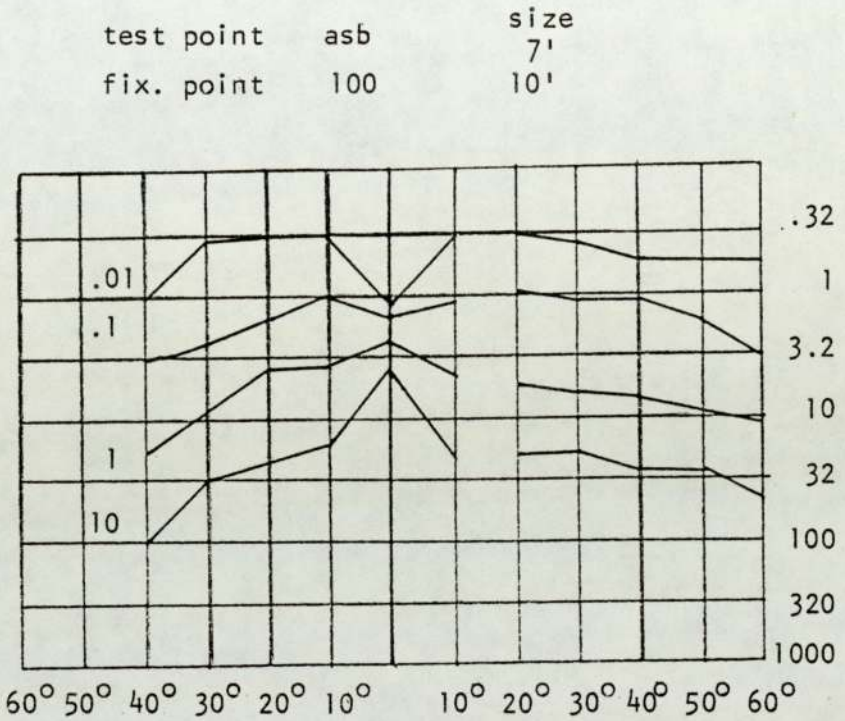


Figure 3.17

Various shapes of static curve obtained in a normal subject with a 7-minute test spot on background of different luminances (luminances indicated on left in asb.). Notice central depression in upper (dark-adapted) curve, a "physiological central scotoma"

(after Ellenberger, 1977)

Static perimetry is influenced by these inaccuracies to a much less degree as the duration of the stimulus is extremely short which means that prolonged fixation is not necessary and the pupillary diameter is not affected by these stimuli; the stimuli appear in random positions, hence reducing the possibility of eye movements.

5. Age

It has been shown by various workers that there is an increase in the minimum discernible luminance thresholds with increasing age, especially after middle age. However, this is not to say, that an elderly person cannot demonstrate a low luminance threshold. This decrease in sensitivity with age has been attributed to a reduction of transparency of optical media, decrease in pupil size, some degeneration of the retina and associated structures. (Friedmann, 1966, 1974; Drance et al. 1967; Lynne and Phillips, 1969; Bedwell and Obstfeld, 1970; Bedwell, 1974).

From the account given above, it can be seen that the advantages of static perimetry outweigh those of the kinetic perimetry in that 1) there is a much better standardisation of stimulus conditions, for example, stimulus intensity, duration etc. which is essential when results have to be compared on repeat sessions and also assessed. 2) it allows accurate quantitative measurements to be made which are very valid when the progress of a disease is to be observed, 3) the time which is required for a careful field examination is shorter than that for kinetic perimetry, 4) the variation in the investigatory method of performing the test is greatly reduced by using the static method, especially since the degree of patient interaction is also reduced, e.g. maintaining long periods of fixation.

Greve (1973, 1975, 1979) divided visual field examination into two phases, that is the detection and assessment phases. The detection phase determines whether or not there is a marked reduction of sensitivity whereby a limited number of presentations employing multiple stimulus presentation is used with greater scanning densities for selected areas, employing threshold or supra-threshold measurements or a combination of them. On the other hand, the assessment (or follow-up) phase cannot be standardised like the detection phase and requires threshold measurements at the points to be tested thus establishing a baseline visual field. In this phase, only certain areas are chosen for more detailed investigation (that is, smaller interstimulus distances) on the basis of the detection phase. It can be seen that both phases necessitate the static method.

3.3.2 Choice of Visual Field Instrument

It was from the comparison of these two methods that it was decided to use an instrument which employed the static method of visual field examination. Since the conditions which are to be studied in this project lead to the development of mostly central (and even peripheral constrictions are present, they enter the central 25^{o} - Harrington, 1971). then a central visual field analyser was chosen because of its large representation of this area, namely, the Friedmann Visual Field Analyser (FVFA)*. The FVFA is a compact instrument which has its own in-built illuminator ring (Figure 4.5). This is an improvement on the

Fincham-Sutcliffe screener which is the other most readily available central VFA. The stimuli are back-illuminated by a single Xenon flash unit which eliminates the problem of unequal illumination of the different stimuli which could occur in the Fincham-Sutcliffe screener because the stimuli are illuminated by different bulbs. The sizes of the stimuli on the front plate are proportionally adjusted so as to compensate for the retinal gradient of sensitivity, although Luddeke and Aulhorn (1977) showed that there is an interrupted increase in size of the test-points which could possibly influence the results; however, their findings referred to the Mark I. Nevertheless, a compromise has to be made for the variation in sensitivity between the nasal and temporal hemispheres because the same front plate is used for testing the right and left eyes. In spite of this, the method of altering the stimulus size to account for the gradient of sensitivity is better than varying the luminance level, as it more closely correlates with the increase in receptive field sizes.

It is known that variability exists between the contrast threshold in a given visual field plot and between individuals. These fluctuations are associated with slight deviations in fixation and head positions, changes in refractive lenses and variations in sensitivity across the retina in each individual (Fankhauser and Enoch, 1962; Bedwell, 1972, 1974; Aulhorn and Harms, 1967; Greve and Wijnans, 1973; Greve, 1979; Liubinas, 1981). However, by employing a method similar to that of Greve (1971) whereby the minimum light threshold is recorded for each stimulus, it is possible to account for the fluctuations within each individual and amongst individuals.

Although Henson (1980) stated that the ideal instrument should have an adjustable illumination system with a light meter in order to compensate for varying room illumination and stray light, this should not present as a significant problem if the visual field examination is carried out in the same room under identical conditions. However, a calibrated photometer is available with the FVFA which determines the intensity of the stimuli so that they remain at the same fixed value.

In spite of these disadvantages of the FVFA, this instrument satisfies many essential requirements for visual field investigation and permits a careful examination to be performed in a relatively short period of time.

A description of the FVFA, Mark I has been given by Friedmann (1966) and Bedwell (1967 a and b; 1972). Over the years, it has become one of the most useful and popular pieces of visual field equipment and as a result of this, many workers have utilised it in several studies. Various investigators have examined the performance of the instrument by comparing it to other instruments in supposedly normal eyes (Linfield, 1970; Greve and Verduin, 1972; Kreiglstein and Andrae, 1975) and in patients with various diseases, especially glaucoma (Greve, 1973; Bynke and Nordenfelt, 1974; Feldman, 1975; Kreiglstein and Andrae, 1975; Hara, 1978; Gutteridge, 1982). Other workers have used the instrument on its own and analysed the results using normals (Greve, 1971) and using patients with known field defects (Friedmann, 1970, Van Dalen, et al. 1981).
In some of these investigations, it was reported that the FVFA failed

to detect small percentages of relative field changes of early onset which were detected by other instruments (Greve, 1973; Bynke and Nordenfelt, 1974; Feldman, 1975; Kreiglstein and Andrae, 1975; Gutteridge, 1982). Greve (1973) concluded that this failure in detection should not be attributed to the method of presentation (as he devised a sensitive method of examination) but to the comparatively small number of stimuli and the large interstimulus distances (although this comment is perfectly valid, it has to be remembered that in a comparison of instruments, one instrument has to be used as the baseline and assumed to yield the correct results). To overcome this problem of too few stimuli, various workers rotated the front plate in order to stimulate the retina in more positions and found it very effective in the detection of lesions (Bedwell, 1971; Shinzato et al. 1977; Friedmann, 1977; Verduin and Bakker, 1982). These criticisms of the FVFA, Mark I lead to the development of a new version of the instrument which has been recently introduced and has been called the Mark II (Freidmann, 1977, 1979). In this new version of the FVFA, the following aspects have been improved: 1) the number of stimuli has been increased from 46 to 98, especially within the central 10^{o} (Friedmann, 1977). The interstimulus distance has therefore been greatly reduced allowing a more accurate assessment of the central visual field. If more stimuli are required, eccentric fixation can be employed but at the expense of time. 2) the groups of stimuli no longer form geometrical patterns which previously allowed patients to memorise them especially since there were so few stimuli.

3) there is a choice of chromatic filters, so that chromatic macular thresholds and campimetry can be done, 4) the instrument offers a range of controls, including a continuous flow of filter selection, illuminated panels etc. which enable easier operation.

Friedmann (1977) showed that whereas the FVFA, Mark I demonstrated a probable early glaucomatous defect, the Mark II showed a deformative ~~accurate~~ arcuate scotoma. A static profile plot along a particular meridian revealed similar areas of depressed function in the FVFA Mark II and the Goldmann Perimeter.

Marmion (1981) compared the FVFA Mark I and Mark II on glaucoma suspects and on patients with glaucoma and concluded that the Mark II fulfilled the role of detection and follow up more accurately than the Mark I. However, if this difference is to be appreciated then the results should be analysed in a more definable manner than the 0.4 log unit criterion from the suggested filter density. This worker summated the filter settings of the whole of the upper and lower fields and compared with the counts from within the corresponding 10^{o} to 20^{o} area from fixation. It was found that in the Mark II, there was a significant difference in both the upper and lower fields between the arcuate area and the whole field in the glaucoma suspects.

Friedmann (1980) and Marmion (1981) used the colour filters on patients with visual field defects and on normals respectively. The former worker felt that although much more work was still needed, it appeared that the stimulus brightness required in pathological areas to coloured

stimuli was greater than that required for white light. The latter worker suggested that the instrument provided a simple method for examining cone function in light and dark conditions.

The FVFA could be criticised in that it only offers set patterns of stimuli and therefore it does not have several arrangements of stimuli for testing specific areas which are likely to be affected in various diseases. However, this should not be a significant disadvantage with the Mark II because of the increased number of test-points. Although Greve, (1975, 1980) has suggested that the optimum number of stimuli should be between 120 and 150 for revealing the smallest clinically significant defects of 3^{o} to 5^{o} in the central field, a compromise is made by employing multiple stimulus presentation which makes use of the "visual extinction phenomenon" and therefore increases the sensitivity of detection.

The accuracy of fixation is sometimes difficult to assess but generally it can be seen when a patient is trying to scan the screen. Henson (1980) pointed out that very accurate fixation can only be obtained by using a dental bite which is not practical clinically and therefore a sacrifice has to be made.

Suzuki and Tomonaga (1979) often noticed that the sensitivity of a single stimulus was decreased in comparison to remaining stimuli whilst testing with the FVFA. They superimposed a chart of the FVFA over a fundus photograph (within central 30^{o}) to see which point corresponded to a retinal vessel. The reduced values for angioscotomata ranged

from 0.2 to 0.8 log units (with 80% eyes lying between 0.2 and 0.4 log units). Nevertheless, this can be overcome by moving the fixation points eccentrically and retesting the stimulus point to see if it still remains depressed.

The effect of pupil size was studied on the FVFA by Bedwell and Davies (1977). The effects of stimulus eccentricity and sex were also considered. It was found that a constricted pupil (3.5mm) had a negligible effect on the light threshold in either sex. However, the threshold was lowest for males with a dilated pupil (9mm) and highest in females with a normal pupil, with a maximum difference of 0.14 log units. The females failed to demonstrate this definite decrease in threshold with the dilated pupil as the males did. With increasing eccentricity from 12.5^{o} to 20^{o}, there was a consistent trend for increased thresholds by up to about 0.1 log units. These workers concluded that although the variation in log threshold is within physiological limits, the effect of the other variables have to be considered and therefore it might be pertinent to take pupil size into consideration, especially in young males with dilated pupils. It was proposed that the lower threshold values illustrated by males at all pupil sizes were due to better performance by males at visual tests whilst females had a better performance at aural tests (the authors did not specify the type of aural tests).

The FVFA could be criticised in that whenever each montage of stimuli is changed, it is possible that the patient could become aware of the apertures being uncovered. However, this should not be a significant problem because if a patient's light threshold is high, it is unlikely that he would notice this, especially since the changeover occurs quickly and the patient does not know which group of apertures will be uncovered.

The Friedmann VFA, Mark II has been chosen because it fulfils most of the requirements of an instrument which allows accurate recording of visual fields, for example, it provides the advantages of static campimetry, it uses multiple stimulus presentation from a single flash etc. In addition to this, it offers a large representation of the central field (25^{o}) which enables more detailed investigation of the central area which is predominantly affected in the patients who are to be observed in this project. It has already been mentioned that several workers have stated that the majority of visual field defects (90-95%) can be detected by central field examination and Ellenberger(1977) and Harrington (1981) have reported that peripheral constrictions are accompanied by an impingement of the central area. In performing the visual field investigation, a more sensitive method of presentation is to be used than that given in the handbook so that the variation in sensitivity within and amongst individuals will be considered. It also has to be remembered that factors, such as pupil size, angioscotomata, can affect the results and they have to be taken into consideration.

3.4 FLICKER ATTENUATION CURVES OF THE HUMAN EYE

Since Greek antiquity, it has been known that an intermittent light stimulus appears to be fused above a certain frequency (Ptolemaeus, approx. 80-160AD). Following Segner's attempt in 1740 to measure the frequency at which the persistence of vision occurred, a colossal number of studies have been performed which relate flicker and fusion. At a given depth of modulation (contrast), the frequency at which the transition from the appearance of flicker to fusion of a flashing light occurs, is called the critical fusion frequency* (CFF). The CFF could be considered as a measure of the temporal resolving power of the eye. Many investigators have observed the behaviour of the CFF under various conditions of stimulation, such as the effect of target size, whilst other workers have used the CFF to examine the integrity of the visual system in pathological conditions. The classical techniques for measuring the CFF, employ stimuli which generally consist of a series of periodical rectangular light pulses separated by dark intervals (Figure 3.18a).

Nevertheless, the abundance of literature on this topic did not prevent a Dutch telecommunication engineer, de Lange (1952, 1958) from developing theoretically and practically a more effective technique (which was previously introduced by Ives, 1922) for investigating the efficiency of the temporal visual system which involved obtaining threshold values of flickering light with a different approach. De Lange decided to apply his knowledge of electronic circuits on the visual system. For testing the properties of an electronic circuit,

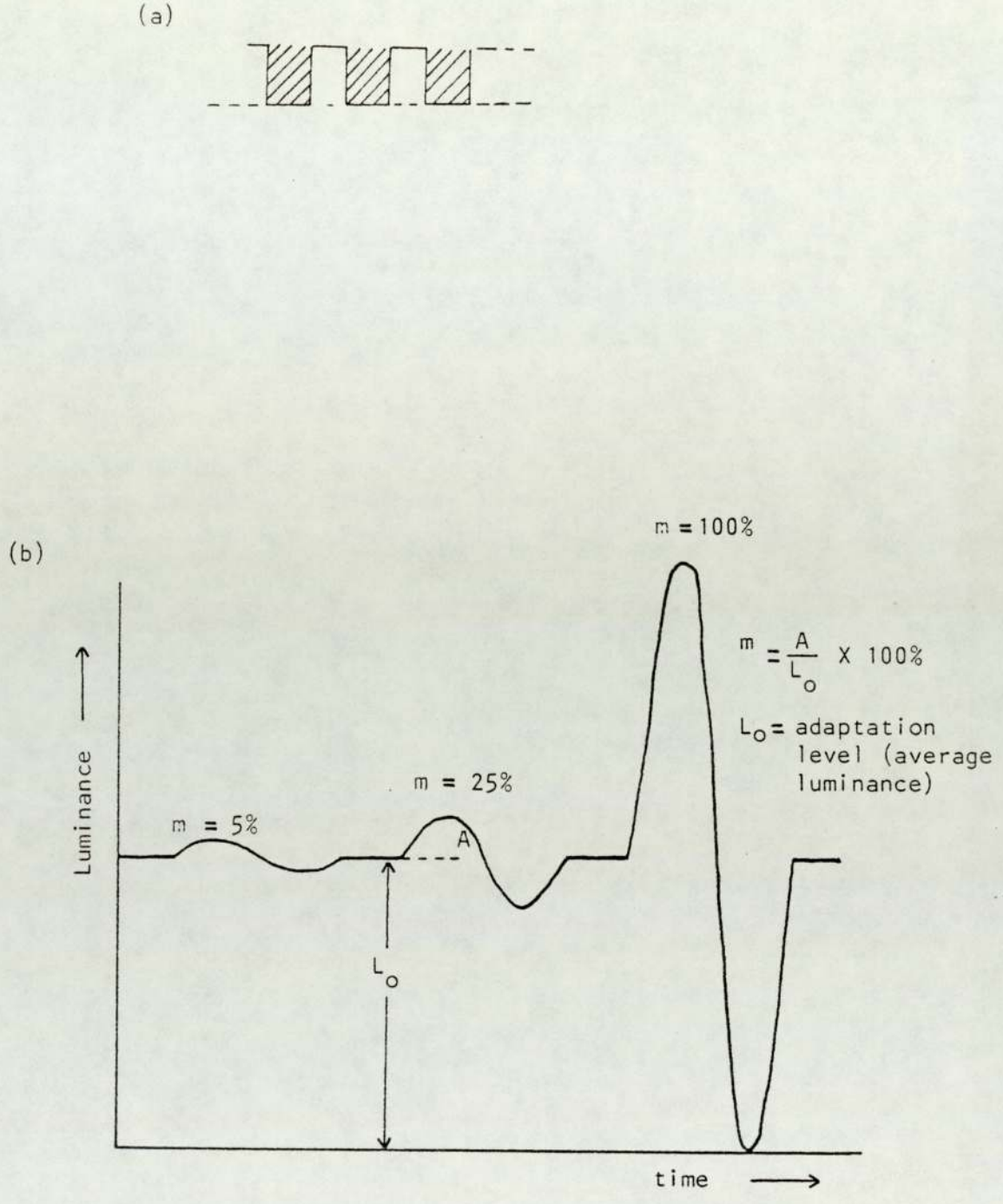


Figure 3.18

(a) Schematic diagram of the light stimulus used in "classical" CFF studies.

(b) Schematic representation of sinusoidally modulated light. For simplicity, only one cycle is presented at different modulation depths. Frequency can be chosen at will.

a method which is often used, is to apply a sinusoidal signal at a certain frequency and then compare the form and amplitude of the output signal to that of the input signal. The ratio of the output amplitude to the input amplitude as a function of frequency is embodied in what is called an attenuation characteristic. This characteristic indicates to what extent the sinusoidal signal is amplified or attenuated more strongly over a part of the total frequency band with respect to another frequency band. De Lange (1958) referred to this as a "filter action" taking place.

It was these principles which de Lange applied to the human eye whereby the input signal was a sinusoidally oscillating stimulus and the output signal was a perceived observation. He found that the visual system acts as a "non-linear" amplifier (that is, it alters the frequency of the input signal) except within the region at which the threshold for flicker fusion is approached when it behaves in a more or less linear manner.

As it is not possible to obtain the amplitude of the output signal from the visual system, de Lange determined the constant output amplitude of the light stimulus which produced a threshold or flicker fusion effect at a particular frequency. In order to do this a sinusoidal light stimulus (input signal) which oscillates about a constant mean luminance level, (that is, it possesses an arbitrary positive value or DC component) is used. The relative amplitude about this mean luminance level is referred to as the depth of modulation (amplitude of sinusoidal change/amplitude of mean level)

which is often expressed as a percentage (Figure 3.18b). The minimum depth of modulation at which flicker fusion is perceived, is known as the threshold value (m) for a given frequency. By obtaining the modulation threshold values at several representative frequencies ranging from the low to high frequency region, it is possible to plot a typical "de Lange" attenuation curve with the threshold modulation depth (m) as the ordinate and the frequency of stimulation as the abscissa (Figure 3.19). This curve demonstrates a maximum sensitivity (reciprocal of m) at about 10 Hz which really indicates the minimum light modulation necessary for fusion, this peak is also called the pseudoresonance peak (Van der Tweel and Estevez, 1974). At lower and higher frequencies a larger increase in modulation depth is required to achieve fusion even more so in the high frequency domain.

It has been found that the depth threshold modulation is altered in a different manner at low (<10Hz) and high (>20Hz) frequencies with changes in the conditions of stimulation. The effect of the conditions of stimulation on the attenuation curves will now be discussed.

3.4.1 The Effect of Physical and Physiological Factors On The Attenuation of Curves.

1. Changes in adaptation level.

De Lange (1958), Kelly (1961) and Breukink and Doesschate (1963), Babel, et al. (1977) showed that a decrease in the adaptational level (L_o, which determines the retinal illuminance if the pupil size is constant), leads to a lowering of the curve; mostly in the high frequency

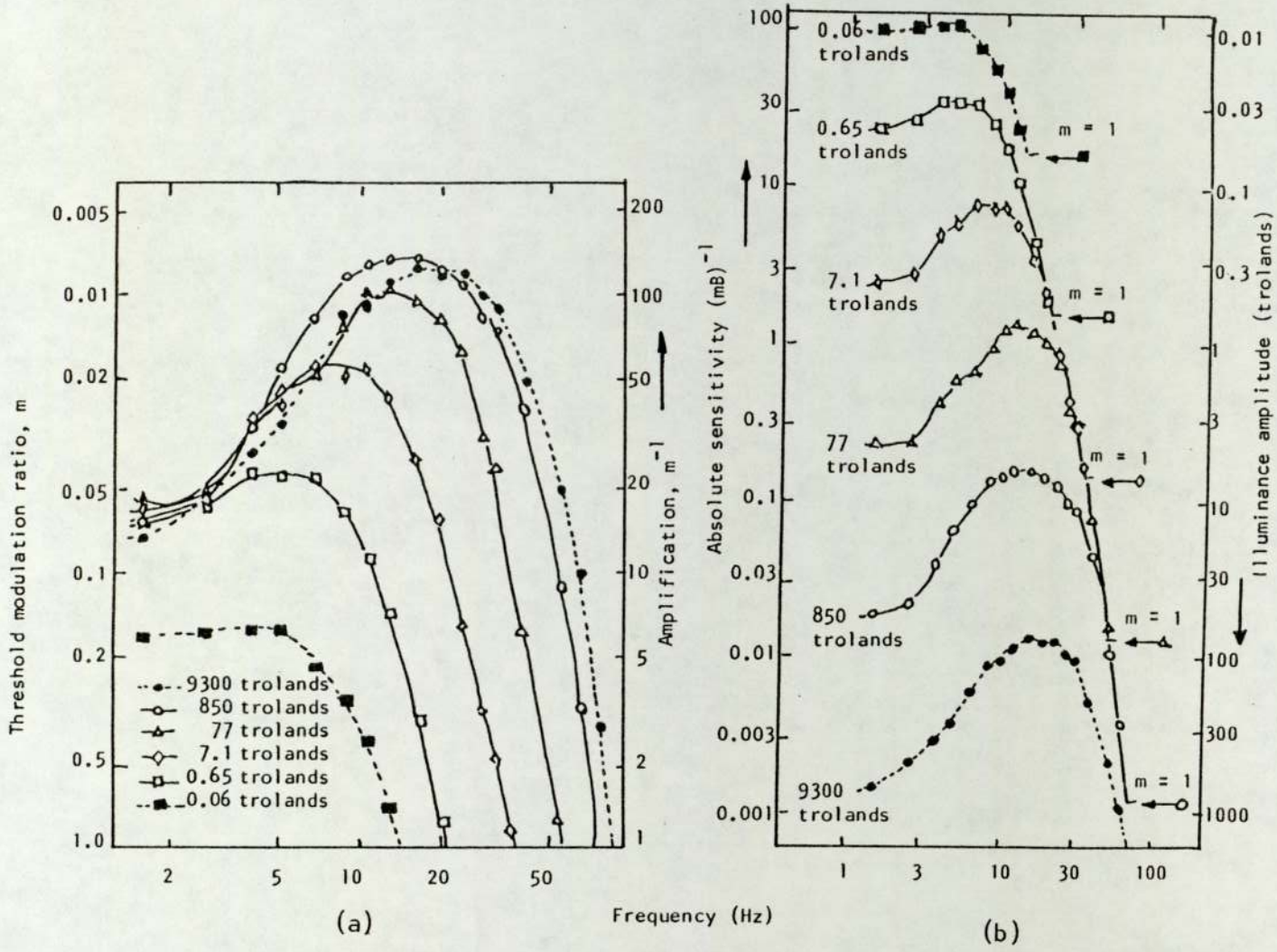


Figure 3.19

(a) Relative amplitude sensitivity versus modulation frequency at six adaptation levels (b) Absolute amplitude sensitivity versus modulation frequency at six adaptation levels (after Kelly, 1964)

region with a gradual disappearance of the peak of maximum sensitivity at scotopic levels (Figure 3.19). It was observed that the modulation sensitivity remained relatively unaffected at low frequencies which suggested that low frequency flicker thresholds are dependent on the modulation depth regardless of adaptational level in the photopic range (De Lange, 1958; Kelly, 1961 , 1964). However, Kelly (1961, 1964) pointed out that there was a better way of representing the high frequency data whereby not only the modulation threshold depth (m) was considered but also the adaptational level (L_o). This was done as (m) could be similar at several adaptational levels (L_o) and therefore (m) alone, was not the only parameter to take into account on analysing the data. Nevertheless, this does not underestimate the useful information obtained in the low frequency domain from Figure 3.19a.

By plotting another graph of absolute threshold amplitude ($m \times L_o$) against the stimulus frequency, it is seen that at high frequencies there is an overlap of the curves forming what Kelly, (1961, 1964) refers to as a master curve (Figure 3.19b). Along this curve, the high frequency threshold depends only on the absolute threshold amplitude whether it is obtained by varying (L_o) or (m) and is in essence, independent of the adaptational level which is a necessary condition for the linear response shown by the high frequencies. In contrast to the high frequencies, the low frequencies did not demonstrate this linearity, since several absolute threshold amplitudes may be just detectable as flicker at a given frequency (that is, as L_o decreases, m also decreases).

The results of Figure 3.19a and b indicate that the threshold mechanism is preceded by an operation which makes it appear to be limited by the relative amplitude (m) at the low frequencies and by the absolute amplitude ($m \times L_o$) at high frequencies, changing gradually from one type of behaviour to the other in the middle frequency range (Kelly, 1961).

2. Size of Test Field

On compiling data from various studies, Kelly (1964) demonstrated that for approximately the same adaptational level in the stimulated area, the size of the stimulated retinal area had a marked effect on the low frequency sensitivity (Figure 3.20). With an increase in stimulus size, there is a reduction in low frequency sensitivity, Kelly (1964) mentioned that these results would be consistent with the hypothesis that some kind of inhibiting mechanism exists among the different regions of the retina. These results are the opposite of most area effects (for example, the ERG). In the high frequency region, the flicker sensitivity increased with increasing field size but it was not as drastically affected as the low frequency domain.

Kelly (1964) wondered if the modulation sensitivity would further decrease with an even wider flickering area or at frequencies less than 1Hz. On comparing his low frequency data to that of Thomas (1962) (who made his subject read a book in a room with sinusoidally modulated lamps), he found that the two sets of data were very similar in the region of overlap but did not agree well with de Lange's (1958) data. Kelly suggested that wide field flicker data was more typical of normal seeing conditions.

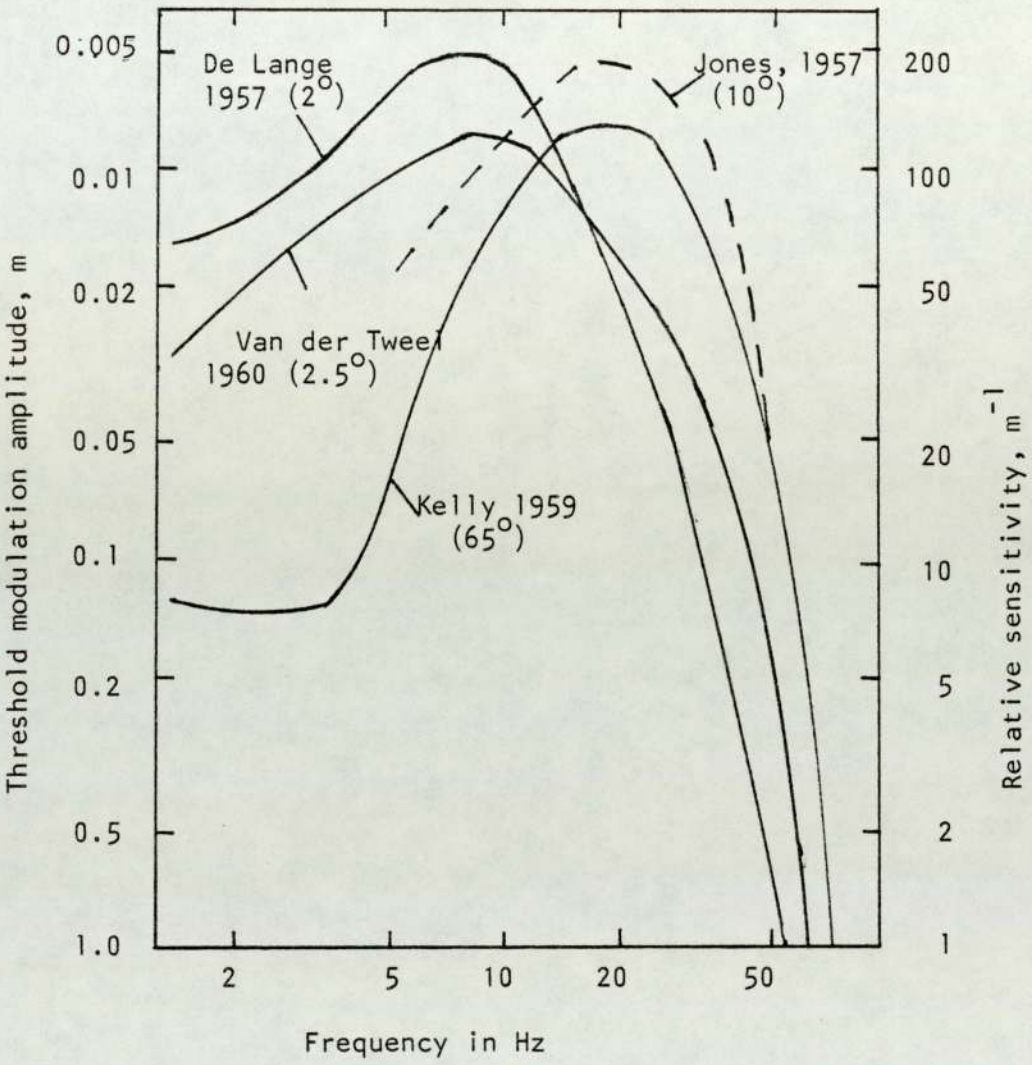


Figure 3.20

Attenuation curves obtained under various conditions at four different laboratories, but with approximately the same adaptation level in the stimulated area. Note that the high frequency sensitivity is relatively unaffected, but there is a systematic decrease in the low frequency sensitivity as the size of the flickering source is increased.

The effects of eye movements on flicker sensitivity was examined by Tulanay-Keesey (1962, 1968) to observe if they had any influence on the comparatively high sensitivities obtained by de Lange (1958) for a 2^{o} test stimulus. It was hypothesised that if flicker was detected mainly by receptor cells around the edges of the small field, then there should be a lower sensitivity with image stabilisation. This worker investigated the modulation thresholds for circular targets ($\frac{1}{2}$ - 4^{o}) from 2.5 to 60Hz, using flickering, non-flickering and dark surrounds. She found that regardless of image stabilisation, the flicker sensitivity curve was affected by field size, mean luminance and type of surround. However, image stabilisation only had a small effect on the flicker response function indicating that eye movements have a negligible contribution to flicker sensitivity.

Kelly (1969a) felt that edge enhancement was not eliminated by image stabilisation. He investigated modulation sensitivity under carefully controlled conditions, using sharp and blurred edges, unstructured circular (3^{o}) and rectilinear (8^{o} x 16^{o}) targets of various flickering and non-flickering areas and gratings of different spatial frequencies (5'-4^{c}; the maximum response was seen at 15' which agreed with the optimal check size for VER pattern stimulation which was associated with receptive field size - van der Tweel and Spekreijse, 1966). He found that at low frequencies the flicker sensitivity increased with the number and sharpness of edges in the target and also by a flickering contiguous surround of opposite phase. He concluded that the reduced sensitivity to wide field stimulation (Figure 3.20) in the low frequencies, was due to the absence of sharp edges near the fovea regardless of the area of flicker. However, high frequency flicker only depended on the areal effect and was independent of edges. To explain the

difference in behaviour between low and high frequencies without the influence of eye movements he assumed that over short retinal distances, lateral inhibition propagates through a low pass filter (<10Hz). He proposed that the data was consistent with the flicker being due to the process of diffusion of photochemicals in the receptor cells although he suggested that flicker detection occurred beyond the inner nuclear layer where lateral inhibition was presumed to take place. (Kelly, 1969a and b).

3. Effect of Eccentricity

Using a 2^{o} flickering stimulus, Breukink and Doesschate (1963) obtained the attenuation curves for eccentric viewing of the target at 7^{o} and 15^{o} respectively, at a mesopic and photopic luminance level. On comparing these findings to those of direct viewing, it was concluded that the peripheral retina was less sensitive than the fovea in the low frequency range, whereas at higher frequencies, the effect of indirect fixation was negligible. This finding was substantiated by Babel et al. (1969) and would agree with the evidence that low frequency flicker tends to stimulate tonic ganglion cells which are concentrated at the area centralis and have smaller receptive fields than the phasic cells. (Gouras, 1980).

4. Wavelength of the Test Field

The shape of the attenuation curves varies with coloured flickering stimuli and surround. By balancing all the colours so that they had equal luminances, De Lange (1958a and b) showed that on progressing from red to blue for a 2^{o} stimulus there was a reduction in modulation

sensitivity with the curve flattening (that is, it lacked a peak sensitivity) on approaching blue stimulation.

Kelly (1962) reported that chromatically adapted responses to white flicker show that the low frequency is controlled by the blue-sensitive channel, middle frequency by the green sensitive channel and high frequency by the red-sensitive channel. It was also observed that the responses to red stimulation were least affected by chromatic adapting stimuli whilst those to blue stimulation were greatly affected.

Green (1969) investigated the attentuation characteristics of colour mechanisms as isolated by Stile's technique. He showed that the blue system demonstrated much lower modulation sensitivity than the green or red mechanism which was in accordance with its lower VA, lower contrast sensitivity and greater spatial summation.

5. Effect of Pupil Size

The influence of decreasing pupil size (8mm to 1.5mm) for a 2^{o} test field lead to a decreased sensitivity of the attentuation curves at all frequencies which roughly corresponded with the loss of retinal illumination (Figure 3.21).

From the results of de Lange (1958) and Kelly (1961, 1964) it would be expected that the high frequency region should be more attenuated than the low frequency region as the low frequencies are mostly dependent on the modulation threshold (m) which should be less affected by a variation in pupil size.

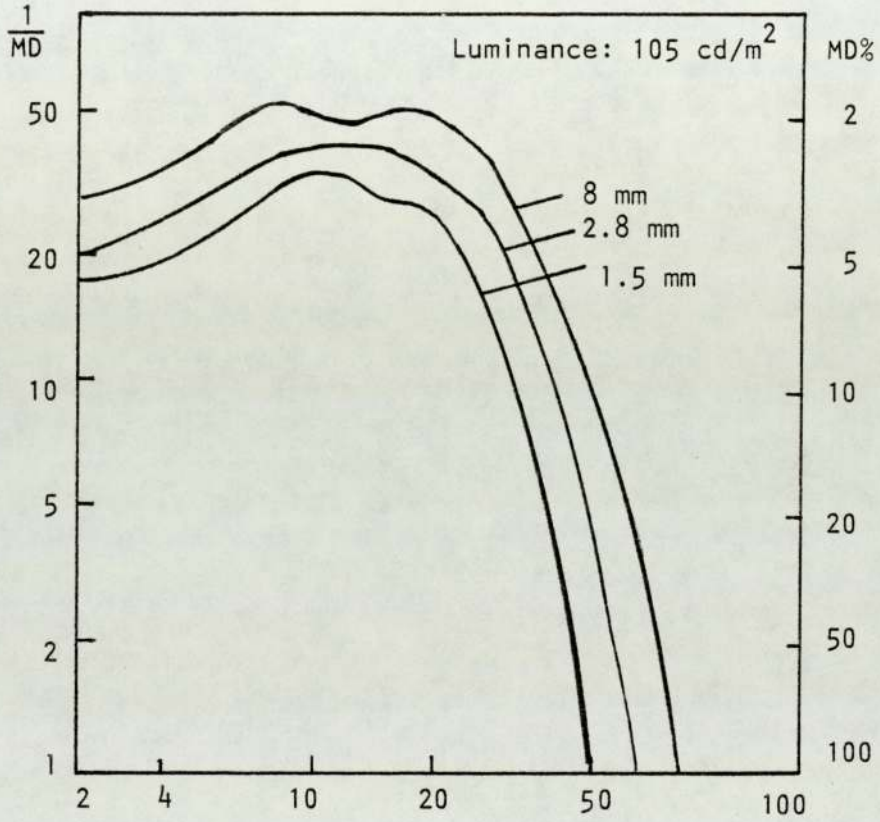


Figure 3.21

Attenuation curves for one normal subject at three pupil sizes. A decrease of the pupil leads to a lowering of the attenuation curve which roughly corresponds to the loss in retinal illumination (after Breukink and Doesschate, 1963).

6 Influence of the general conditions of the subject and inter-individual differences between normal subjects.

Breubink and Doesschate (1963) reported that there was only a slight lowering in modulation sensitivity when one subject was repeated in a tired condition, who was previously tested in an alert condition. The results of 20 normal observers lead the above workers to state that differences between the curves expressed themselves mainly in the level of the curve and not in its form.

3.4.2 Flicker Sensitivity in Relation to the Retina and Visual Pathways.

It can be seen that the low and high frequency regions of the attenuation curve exhibit different properties under identical stimulus conditions. For this reason, Kelly (1964) hypothesised that there were at least two different retinal mechanisms accounting for the dissimilar behaviour. He also proposed a one-stage model whereby flicker detection occurs in some retinal layer although he could not be sure as to which one is responsible. There is also electrophysiological evidence which supports the hypothesis that flicker sensitivity is at least partly retinal. Cleland and Enroth-Cugell (1966) recorded from single ganglion cells of a cat's retina whose receptive fields were stimulated by small spots of sinusoidally modulated light. They found that the attenuation curve of an on-centre cell demonstrated a peak at about 6 Hz and resembled the human pyschophysical curve in form. This study depended upon the ability of the experimeter to detect the discharges aurally.

Ratliff, et al. (1967) recorded the frequency of impulses from the ommatidia of the compound eye of the horseshoe crab and observed that when the modulation depth was kept constant in each case and the stimulating frequency was varied, the curve had a similar shape to the human curve although it peaked at approximately 3Hz. On increasing the size of the stimulating spot, there was an increase in the maximum discharge rate of the ommatidia at higher stimulus frequencies. In addition to this, the frequency of stimulation had to be raised from 2.5 to 5 Hz. in order to elicit the maximum response. On the other hand at lower stimulus frequencies, an increase in field size caused a decrease in the discharge rate which parallels low frequency behaviour of the attenuation curve. These authors suggested that lateral inhibition must be responsible for this as it is the only significant form of interaction in the ommatidia. On abolishing postreceptor potentials with sodium asparate, Baron and Boynton (1973) observed the local ERG from the foveal cones during stimulation by sinusoidally modulated light of various frequencies. At photopic levels they found that no recognisable ERG was seen until a frequency of 20Hz had been reached. It was concluded that the reduction in low frequency sensitivity seemed to result from postreceptor inhibitory mechanisms, and not from the cones.

In contrast to Kelly's (1969, a and b) hypothesis of a one-stage process, Van der Tweel and Estevez (1974) postulated that the steep fall in the high frequency range is a result of the action of a number of subsequent stages which each attenuates the high frequencies. They believed that this was more likely than a one-stage model for certain reasons, such as, for increasing frequencies the psychophysical fall in sensitivity is larger than that for the

electrophysiological amplitude. They also felt that excessive attenuation due to a spread in latency (as suggested by Kelly) became a more plausible process in pathology where variations in speed of propagation are thought to be larger, which could be the case in retrobulbar neuritis.

In relating the temporal properties of flicker sensitivity to the types of cells stimulated, Gouras (1980) reported that phasic cells were generally more sensitive to high frequency flicker than tonic cells.

3.5 Summary

On considering the signs and symptoms of the conditions which are to be studied, the above tests have been selected for investigation. The ERG is a useful tool in detecting retinal changes in many diseases (Babel et al. 1977; Galloway, 1981). However, there have been varied reports as to whether it is one of the early detectors of the conditions listed. Like the ERG, the VER is also a non-invasive objective technique which requires less patient co-operation than the psychophysical tests and it has been shown to be sensitive in assessing the functional state of the optic nerve (Babel et al. 1977; Halliday and Mushin 1981; Harding et al. 1980, 1982; Galloway, 1981; Reimslag et al. 1981). Pattern colour opponent stimuli are also to be incorporated in the testing procedure. These pattern stimuli have been found to be effective (more so than flash stimuli) in detecting colour disturbances and ~~have~~ have been used by comparatively few workers for congenital defects. (Regan and Sperling, 1971; Regan, 1972, 1977; Regan and Spekreijse, 1974; Spekreijse and Van Der Tweel 1974; Dixon, 1981). The conventional methods of colour testing involves the use of three or more tests to ascertain 1) whether a colour defect is present, 2) the type of defect, and 3) the severity of the defect.

It is hoped that by using coloured pattern stimuli for VER recording these three requirements can be fulfilled without having to employ many colour vision tests which are in most instances designed to detect congenital disturbances. In addition to this, the VER is able to indicate the neurological function of the visual pathways without further investigation.

The assessment of the visual fields is a well-accepted clinical method for observing the presence and course of ocular disease. It is to be noted if this test provides results which are comparable to those of the other tests, or does one or more of these tests respond more effectively in a particular disease, hence indicating which aspects of the visual mechanisms are affected. For this reason, the examination of threshold flicker modulation had been included, as well as to observe if it can be a helpful diagnostic tool. The routinely recorded Snellen letter acuity - (which is a function of the foveal and macular regions and is limited by the spatial organisation of the retina) for distance and the Keeler near 'N' series acuity are also to be taken. Meyer et al (1974) found that flicker modulation thresholds were more useful than VA in detecting and quantifying macular and perimacular field losses, whilst Verriest and Uvijls(1977) reported that foveal static thresholds for monochromatic stimuli were abnormal in a large number of patients who demonstrated clinically normal VA and colour vision (anomaloscope, panel D15 and pseudoisochromatic plates), suffering from retinal and optic nerve diseases. Skalka (1980) demonstrated pattern VERs were more sensitive than VA in assessing optic nerve damage. From these studies and those in Chapter 2, it would appear that the VA measurement would not be adequate in detecting early visual changes.

CHAPTER 4

METHODS OF INVESTIGATION

METHODS OF INVESTIGATION

4.1 General Method

The battery of electrophysiological and psychophysical tests which has been chosen to be used in this project (Table 4.1), has been performed on 60 volunteer subjects (29 males, 31 females) who were found to be visually clinically normal and were refracted within the past year. Each normal subject under 60 years of age had a distance Snellen acuity of at least 6/6 (6/9 for subjects of 60 years and over) and an 'N' series near acuity (at 38 cm) of N5 in each eye. The pupil size of each eye was noted under test room illumination ($16.5 cd/m^2$) and spectacle corrections were worn when necessary. The refractive corrections ranged between -4.75DS to +4.50DS with an astigmatic component of not greater than -1.50DS in any of the subjects. Only 5 subjects (8.3%) smoked between 10-15 cigarettes per day and 3 subjects drank between 0.6-1.7 litres of beer or lager per day; the other subjects were occasional drinkers.

The normal subjects, who consisted of University staff and students and members of the general public, have been divided into 6 ten year age groups with 10 persons in each group, commencing with the 20-29 age group. In addition to this, 10 subjects from the Asian, West Indian, and African population have been examined and their results have been compared to those of 10 age and sex-matched Caucasians (see Appendix 3). One half of the subjects started with the electrophysiological tests and the other half began with the psychophysical tests in order to reduce the effect of fatigue on either set of results.

In addition to the tests which were carried out on the normal subjects,

Electrophysiological Tests

1 Dark-adapted low-intensity ERGs and photopic ERGs to flash stimuli

2 VERs obtained to flash, pattern reversal and pattern onset-offset stimulation. The pattern stimulation is recorded to black/white, red/green and blue/yellow check combinations

Psychophysical Tests

3a Examination of the central visual fields (25^{o}) to white light, using the Friedmann VFA, Mark II

3b Assessment of the macular thresholds to white, red, green and blue lights

4 Determination of the threshold flicker modulation at three different frequencies, representing the low (3Hz), medium (10Hz) and high (30Hz) frequency range

5 The screening test plates of the Ishihara and HRR pseudo-isochromatic plate tests and the Panel D-15 test (on normals only)

Table 4.1 giving the list of electrophysiological and psychophysical tests which have been used in this project.

the patients who participated in the study, were given an ophthalmoscopic examination on each investigation and their case histories were taken. The patient population was composed of the following groups:

1) Twenty one chronic alcoholics (17 males, 4 females, $\bar{x}=39.6 \pm 8.5$ yr.) from the Rehabilitation Unit of the All Saints Hospital
2) Seven patients (7 males; $\bar{x}=56.9 \pm 9.7$ yr.) suffering from tobacco-alcohol amblyopia from the Birmingham and Wolverhampton Eye Hospitals
3) Fifteen tuberculotic patients (5 males, 10 females; $\bar{x}=31.9 \pm 12.7$ yr.) from the East Birmingham Hospital
4) Six patients (4 males, 2 females; $\bar{x}=51.5 \pm 10.8$ yr.) suffering from ocular toxicity caused by anti-tuberculotic drugs (Ethambutol and Isoniazid)
5) Eight patients (4 males, 4 females; $\bar{x} = 50.1 \pm 13.8$ yr.) suffering from West Indian amblyopia from the Birmingham Eye Hospital.

The tests were repeated at various intervals on each set of patients. In the case of the chronic alcoholics, the first investigation was performed at least 24 hours after hospital admission (so that they were sufficiently alert) but preferably before the patient had received any medication. The second investigation took place at approximately 8 weeks after the first one, when the alcoholics were nearly at the end of their hospital "detoxification" period. Any patient who suffered head injury within the previous 6 months was excluded from the study. On this patient group, an additional test was used to

examine their colour discrimination, that is, the HRR pseudoisochromatic plate test, to observe if any colour defects seen might be possibly of a congenital rather than acquired nature.

The patients who were receiving treatment for tuberculosis, were examined on three different occasions. As Ethambutol was most likely to give rise to ocular changes out of the three drugs (Ethambutol, Isoniazid and Rifampicin) used for tuberculotic therapy, the method of investigation was organised according to the period of administration of this drug. Hence, the first investigation took place before any medication had been given; the second investigation was performed during the period of administration of all three drugs and the third investigation took place after the cessation of Ethambutol but during the continued administration of the other two drugs. The second investigation was carried out about 8 weeks after the initial investigation, as Ethambutol was usually stopped after this period and by this time, this drug should have had its maximum effect. Due to circumstances beyond the experimenter's control, the visual fields of these patients were not examined on the first occasion.

The patients who had been diagnosed as having tobacco-alcohol amblyopia or ocular toxicity due to antituberculotic drugs, were examined shortly after diagnosis and repeated at about 8 weeks afterwards. The patients with "West Indian" amblyopia were treated only once after diagnosis as their condition seemed to remain fairly stable.

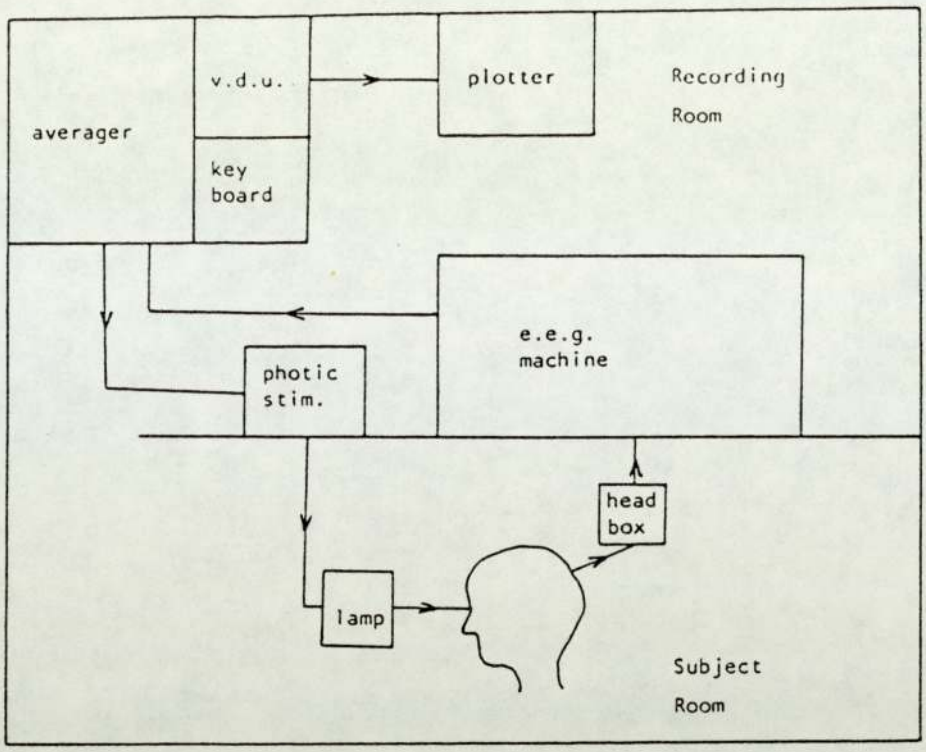
Repeat examinations were carried out at the same time of day as far as possible to control for possible circadian variations and the order of testing was identical to that of the first investigation in order to control for order of presentation.

4.1.1 Method for Electrophysiological Testing

Standard silver-silver chloride electrodes were applied to the scalp with collodion and to the face with adhesive discs, maintaining the resistance of the skin electrode interface below 5Kohms. Four electrodes were placed on the scalp according to the 10-20 International system, that is, O2, O1, C4, C3, whilst two others were each positioned at a distance of 5% (with respect to each outer canthus) of the measurement made from one outer canthus to the other, encircling the back of the head. These latter two electrodes were used as earth electrodes during the recording of the VERs and were changed to reference electrodes during the recording of the ERGs (plugged into F8 and F7 respectively). The head measurements were noted for subjects who were repeated.

The following electrode linkages were employed, O2 - C4 and O1 - C3 (GLE in right eye) (GLE in left eye) for VER investigations and F8 - Fp2 and F7 - Fp1 for ERG investigations. The input from the electrodes were amplified by a 16 channel Elema-Schonander EEG machine which was set at certain specifications depending on the type of response being monitored. The output was then fed into an averager (PDP8E computer) and an oscilloscope (Tetronix, type 611) and a write-out was made using an X-Y plotter (Bryan's X-Y recorder) (Figure 4.1, 4.2).

For VER investigation, the analysis time was 500 ms with a sampling rate of 2 ms and the number of sweeps being 50. The bandpass of the equipment was from 3Hz (TC - 0.3s) to 30Hz and the gain was 100uV/cm. For the dark-adapted ERG and the photopic ERG, the analysis time was 100 ms with a sampling rate of 97 us. However, the number of sweeps were 4 and 25 respectively. The bandpass of the equipment was



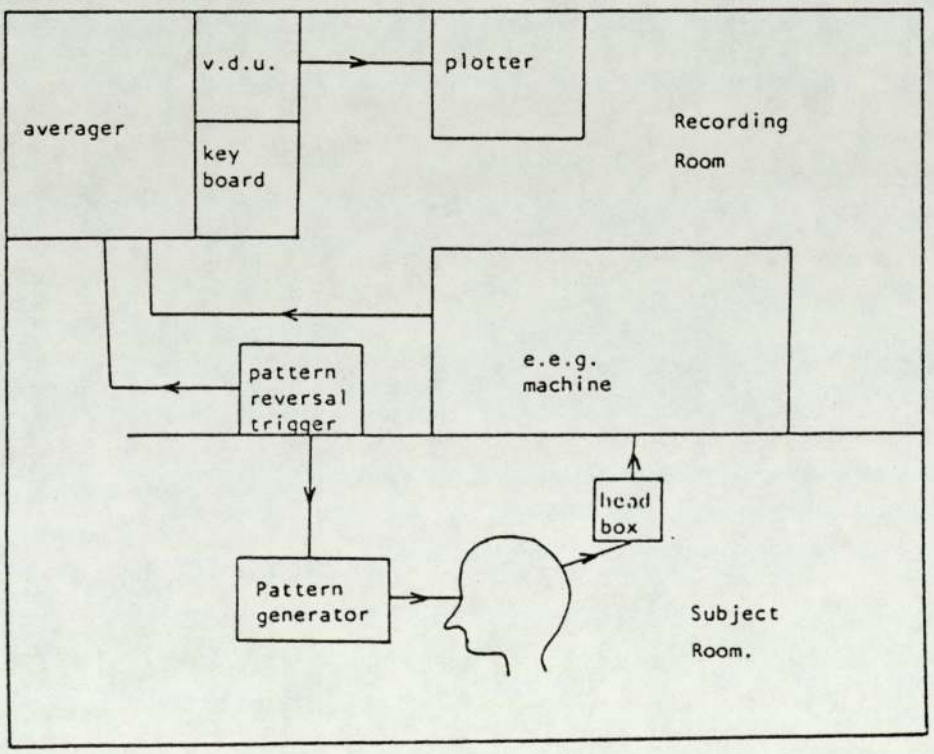


Figure 4.1

Diagrammatic representation of the layout of the equipment used for recording the visual evoked responses to flash and pattern stimulation and the electroretinograms to flash stimulation.

Figure 4.2

A photograph showing the equipment used for the recording of ERGs and VERs. From right to left, the PDP8E computer, the oscilloscope (top), the VDU (bottom) and the X-Y plotter

from 3Hz (TC-0.3s) to 70Hz for the dark-adapted ERG and from 6.7Hz (TC-0.15) to 700Hz for the photopic ERG. The gain was 200uV/cm for both types of ERG (see Appendix 1). The VERs were recorded before the ERGs in order to obtain a constant state of light adaptation prior to dark adaptation.

The EEG activity was observed during recording sessions in order to ensure 1) the absence of mains interference, 2) any electrode artefact and 3) the alertness of the subject.

Recording of the VERs

The subject was comfortably seated 45cm from a translucent screen on which the pattern was projected from the rear. The position of the projected image from a transparency, was varied by means of a rotatable mirror mounted on a pen-motor. The subject was adapted to the diffuse room illumination (16.5cd/m^2) during electrode placement.

The method of pattern onset-offset stimulation was initially employed whereby a pattern of black and white checkerboard squares (contrast of 79.3%) appeared for 150 ms and disappeared for 500ms, maintaining the same overall luminance (1200 cd/m^2) on the screen. The entire stimulating circular field subtended an angle of 25^o, with each check subtending an angle of 56' to the subject's eye. The subject was requested to fixate a small red spot in the centre of the field whilst the responses were being averaged. After the VERs were recorded from stimulation of each eye to the black/white 56' checkerboard pattern, then the stimulation was changed to a red/green equiluminant 56' checkerboard pattern (410cd/m^2) of the same field subtense. The procedure was repeated for the following stimuli:

1) blue/yellow 56' checkerboard pattern; 25^{o} field

2) black/white 14' " " 3^{o} field

3) red/green 14' " " 3^{o} field

The patterns were presented in random order on the first occasion and then replicated on each subsequent occasion for that subject. The angular subtense of the field was altered by using black cardboard templates in front of the translucent screen. The red fixation spot was changed to a blue one for blue/yellow stimulation.

After the pattern onset-offset stimulation was completed, pattern reversal stimulation was presented, using the same stimuli. The difference with this type of stimulation was that the adjacent squares rhythmically exchanged their positions twice per second. In order to diminish the effects of saturation and fatigue, the subject was instructed to look away as soon as each set of responses was averaged and the stimulus was turned off during the periods between trains of stimuli.

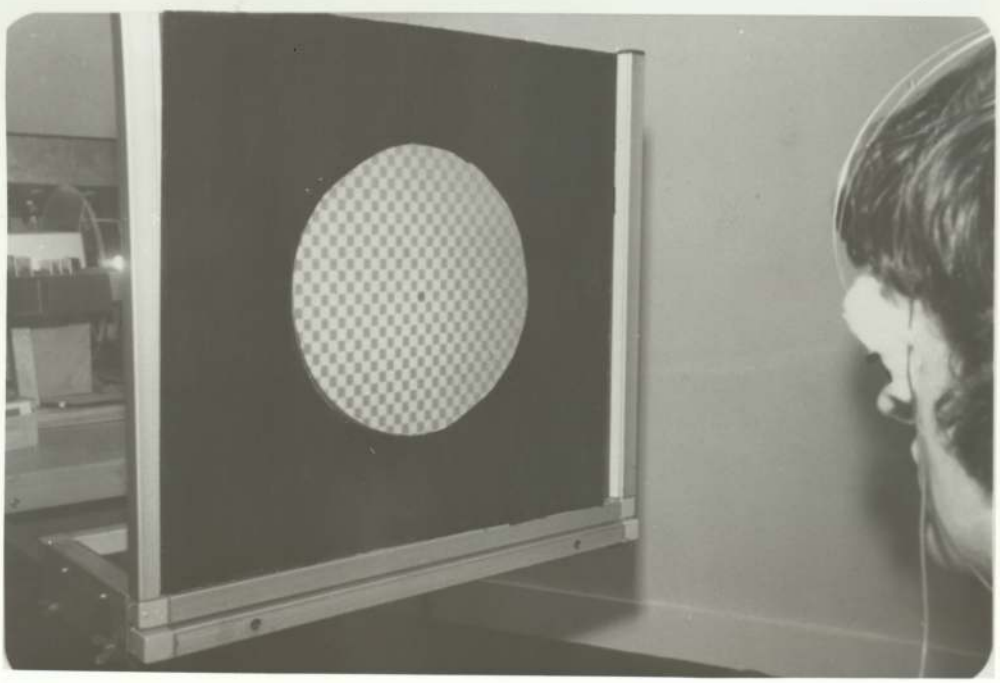
Pattern reversal stimulation was followed by flash stimulation provided by a Grass PS22 photostimulator placed at a distance of 30cm from the subject, giving an angular subtense of 23.5^{o}. The VERs for binocular and monocular stimulation were obtained at intensity 2. (Figure 4.3.).

Recording of the photopic and dark-adapted ERGs.

A drop of 0.4% Benoxinate was instilled into the lower fornix of each eye in order to prevent tearing and excessive blinking on inserting the gold-leaf electrode (GLE). The GLE is constructed from a thin Mylar sheet on to which a layer of chromium and then gold have been implanted. Its total thickness is 25.4um and its width is 4mm. The

Figures 4.3 (a) and (b)

A subject fixating the central spot during (a) flash VER stimulation (b) pattern reversal stimulation



GLE is well-tolerated and does not disturb the optics of the eye. After assuring the patient that no pain would be experienced with the GLE inside the eye, then the lower lid was gently pulled down and the GLE (which was already bent to hook over the lower lid) was placed as far as possible into the lower fornix with the gold side showing upwards. The wire attached to the GLE was bent into a curved loop and taped on to the cheek (Figure 4.4). The subject was asked to fixate a red spot in the centre of the circular screen of the photostimulator, positioned 30cm from the subject. The GLEs were placed centrally with respect to the pupil of each eye and made contact with the corneoscleral junction. A pair of black-rimmed goggles with diffuse opal lenses and side flaps was placed on the subject's face in order to produce equal stimulation of the whole retina and reduce the effect of stray light.

The photopic ERG was first recorded by inserting a red cellophane filter (Kodak Wratten, No. 29) into each lens of the goggles and then starting the flash stimuli (intensity 16).

After the recording of the photopic ERG was completed, the period of dark adaptation (10 minutes) commenced. Prior to presenting the stimuli, the experimenter switched on a red lamp in the subject room and positioned the GLEs. Four single flash stimuli (intensity 2) were separated by a 10 second interval in order to retard the process of light adaptation and preferably stimulate the rods.

The pupils were not dilated by a mydriatic because it would have caused considerable inconvenience to the patients, in addition to other risks.

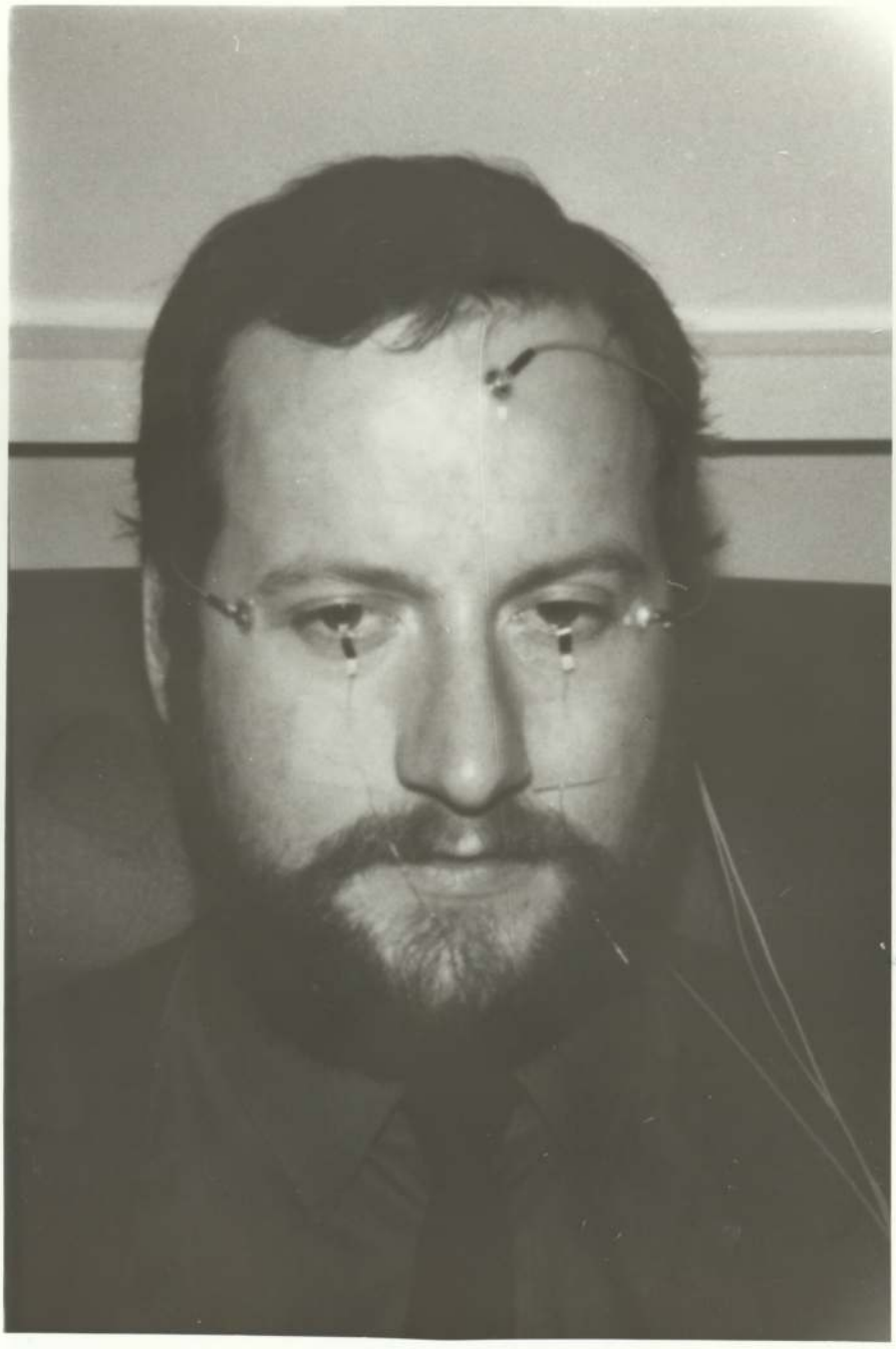


Figure 4.4

A photograph showing the position of the gold leaf electrode in the lower fornices, used for ERG recording

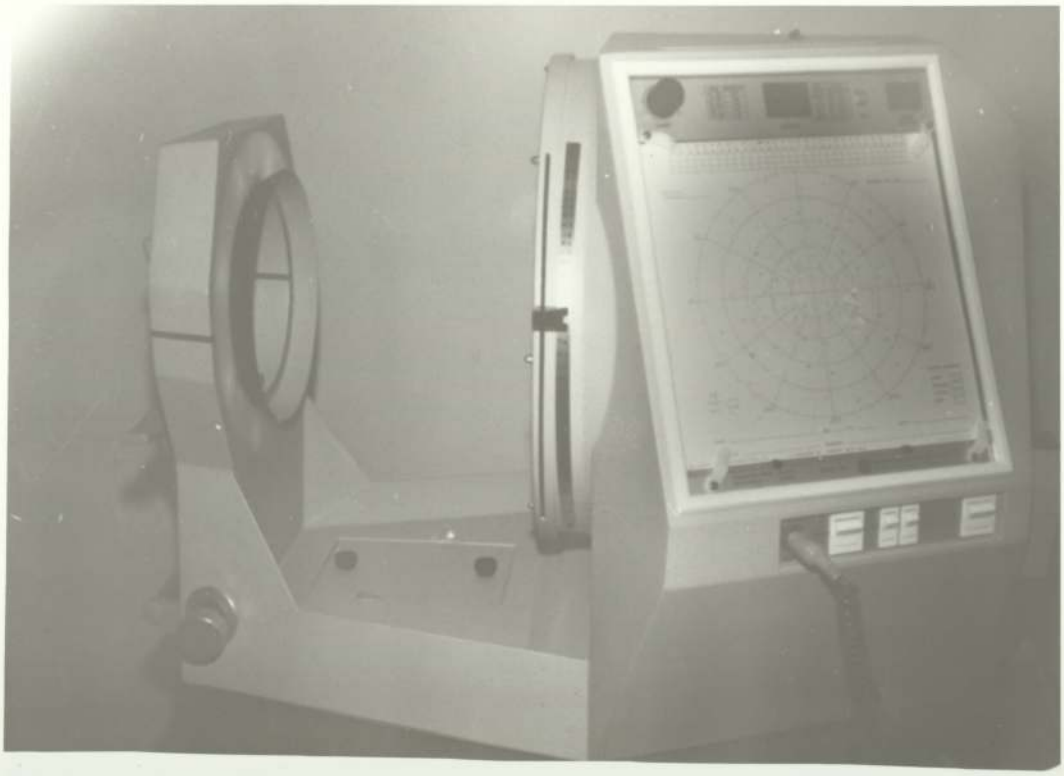
4.1.2 Method for examining the central visual fields, using the Friedmann Visual Field Analyser, Mark II

Determination of the macular threshold

The subject was requested to position his chin on the appropriate chin rest, after one eye had been occluded. His eyes were made level with the central black guide lines across the side of the external illuminator (Figure 4.5). The fixation target was removed from the central aperture when a small white circle surrounding the hole became visible. The macular threshold ring was placed over the central boss to obscure the other stimuli which were simultaneously illuminated with the central stimulus on pressing the trigger.

The test was performed in a darkened room with external illumination being provided by the illuminating ring (2.5 cd/m^2). After the subject had adapted to this level of illumination for 5 minutes, he was instructed to look into the central hole (subtending 20.8') and asked to indicate whenever he saw a light flash by responding with the word "yes" or by tapping his hand. At each filter dial position, the stimulus was presented three times and if no response was obtained, then the filter reading was decreased by 0.2 log units. The filter density at which 8 out of 10 presentations were seen, was taken as the macular threshold.

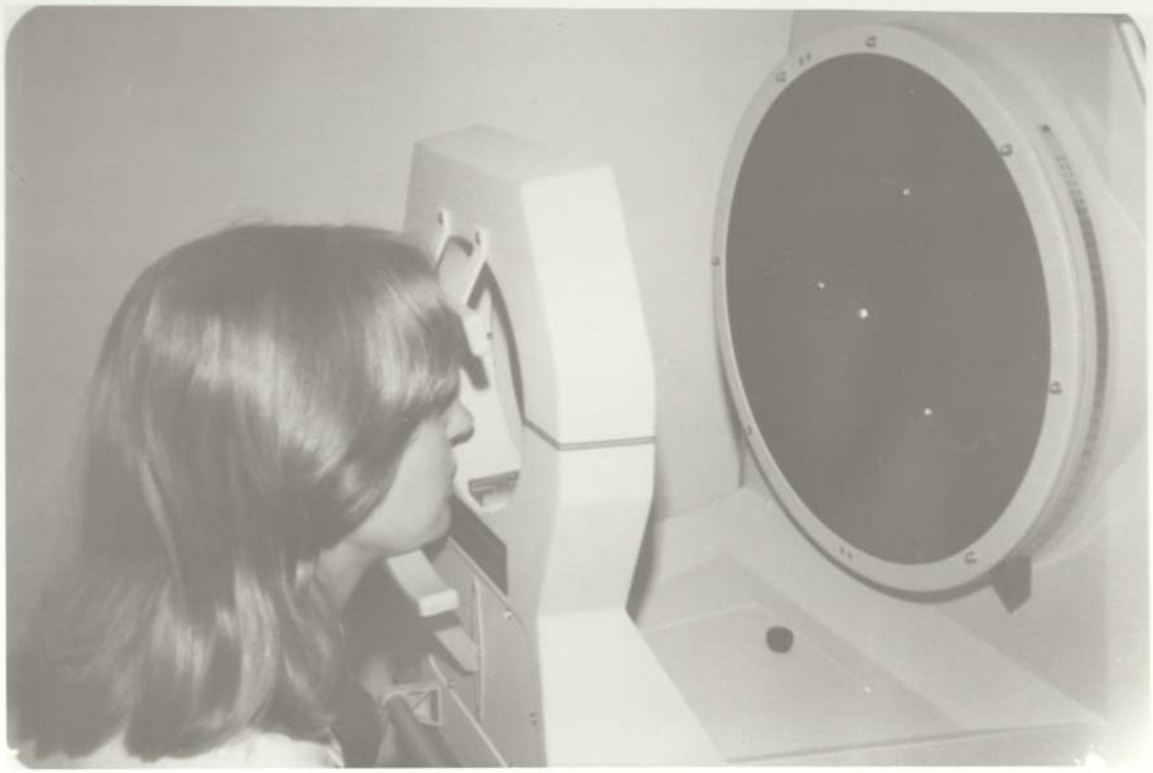
Initially, the macular light threshold to blue light (Kodak Wratten, No.47B) was determined, followed by red (No. 29) green (No. 58) and white stimulation respectively for each eye.



Figures 4.5 (a) and (b)

(a) The Friedmann visual field analyser

(b) The subject fixating the central fixation spot on the front screen whilst the visual field was plotted



Examination of the central visual field

After the macular thresholds had been obtained the visual field to white light was examined after a 5 minute rest period. The smallest white fixation target (subtending 20.8) was placed in the central aperture and where problems were experienced in maintaining fixation with this target, a larger one was used.

The subject was instructed to fixate the central target whenever the experimenter indicated that he was ready to present the stimuli by pressing the trigger button when a short "buzz" was heard. It was explained to the subject that the light flashes which follow the "buzz" appeared and disappeared rapidly and he should report the number of stimuli seen at each lever position from A to h. The subject was also told whether the first montage of stimuli would be presented in the centre or periphery of the screen. After about every ten presentations, the subject was asked to glance from side to side, to reduce the effects of fatigue.

Although certain filter settings were recommended for testing different age groups in the handbook, it had been decided to use filter densities which were 0.6 log units higher than those suggested for each age group (see Appendix 2).

Before commencing the proper test, the subject was given a trial run using 3 or 4 montages at a filter setting of 0.4 log units below the testing density. On starting the test, as soon as the subject had seen one or more stimuli in each montage, he was then asked to verbally indicate their position on the screen. Any stimulus which was not seen

was underlined on the "31-position" chart. The test was repeated at these positions where stimuli had been previously missed and the new lower filter reading was noted. This procedure was repeated until all stimuli had been seen or the "zero" density was reached. If after three filter densities had been presented all the stimuli had not been seen, then the other eye was tested, returning to the previous eye afterwards.

If no stimuli were seen in a montage, possibly due to a lack of attention (less likely to occur because of the buzzer) or a blink, then it was presented once more in order to prevent false positives. During this period of investigation, a check was constantly made on the patient's fixation. As a random check, the patient was sometimes asked to indicate the positions of the stimuli although the correct number had been given.

Subjects were asked to wear their appropriate spectacle corrections when needed and if the frame was likely to reduce the field of view, then wide aperture lenses were used in the auxilliary lensholder supplied with the instrument.

4.1.3 Method of determining the threshold flicker modulation

The flickering source which was a light emitting diode (of wavelength 588nm), was placed behind a small circular aperture which had an angular subtense of 2^{o} to the subject's eye. The flickering stimulus produced was of sine wave voltage and its luminance varied so that the difference between its lowest and highest settings was equivalent to a change in flicker modulation of 30% (see Appendix 4). The small

circular aperture was surrounded by a square screen of approximately the same colour as the light emitting diode and it was sufficiently large and sloped so as to cover the whole visual field of the subject and to provide a constant level of light adaptation (85 cd/m^2) (Figure 4.6).

A +6DS lens was mounted on to a black bar which in turn was fixed at a viewing distance of 16.7cm from the flickering stimulus. This bar was designed so that one of the subject's eyes viewed the flickering source behind the focussing lens and the other eye was occluded (Figure 4.6).

The modulation threshold to flicker was determined for each eye alternately at three frequencies, that is, 3, 10 and 30Hz, representing the low, medium and high frequency regions. The subject was shown the appearance of the flickering stimulus at each frequency before any readings were taken. Six threshold readings were obtained at each frequency employing the method of limits (Woodworth and Schlosberg, 1966) whereby three readings were taken from "non-seeing to seeing" and the other three were taken from "seeing to non-seeing". This method allowed for a relatively fast assessment of the threshold. The knob for altering the modulation of the flicker, was adjusted by the experimenter so that no cues from motor skill could be obtained. The effects of habituation and anticipation were reduced by turning the knob to different starting positions on the modulation dial.

Half of the subjects started with the right eye in order to minimise any bias of results. After each eye was tested at one frequency, the frequency was changed before testing the other eye in order to reduce the effect of adaptation to a particular frequency. The subjects wore their distance spectacle correction when needed.

Figure 4.6

Photograph showing a subject viewing the 2^{o} flickering stimulus (surrounded by a screen of approximately the same colour) through a +6DS lens whilst the other eye is occluded.

CHAPTER 5

RESULTS AND DISCUSSION

5.1 Normative Data

5.1.1 Electrophysiological Results

The typical waveforms of the dark-adapted low intensity ERG and the photopic ERG which have been recorded in this study are shown in Figures 5.1a,5.2a. From the waveform of the dark-adapted ERG, it can be seen that the rod system is more actively stimulated than the cone system, in that the scotopic part of the A wave (As) is more prominent than its photopic counterpart which is absent in many cases (43.6%). The B wave also portrays a slower-rising slope which is characteristic of the scotopic system. No OPs were seen on these traces even when the low pass filter was sufficiently increased. In contrast to the dark-adapted ERG, the photopic ERG demonstrates a much sharper A wave, with a steeper slope for the ascending B wave on which two OPs are superimposed.

The results of the dark-adapted and photopic ERGs are given for six separate 10-year age groups, (with ages ranging from 20 - 77 years) in Table 5.2, 5.3. These results have been analysed by one-way analysis of variance (ANOVA) for unrelated samples (Witte, 1980 , also see Appendix 5, Table 16). The components of the dark-adapted ERG which have attained significance with progressive age changes are the peak latencies of the A and B waves ($p<0.05$ and $p<0.01$ respectively) and the amplitude of the AB configuration ($p<0.05$). A similar trend is observed for all of the components of the photopic ERG, although these results tended to attain a higher significance level than those for the dark-adapted ERG.

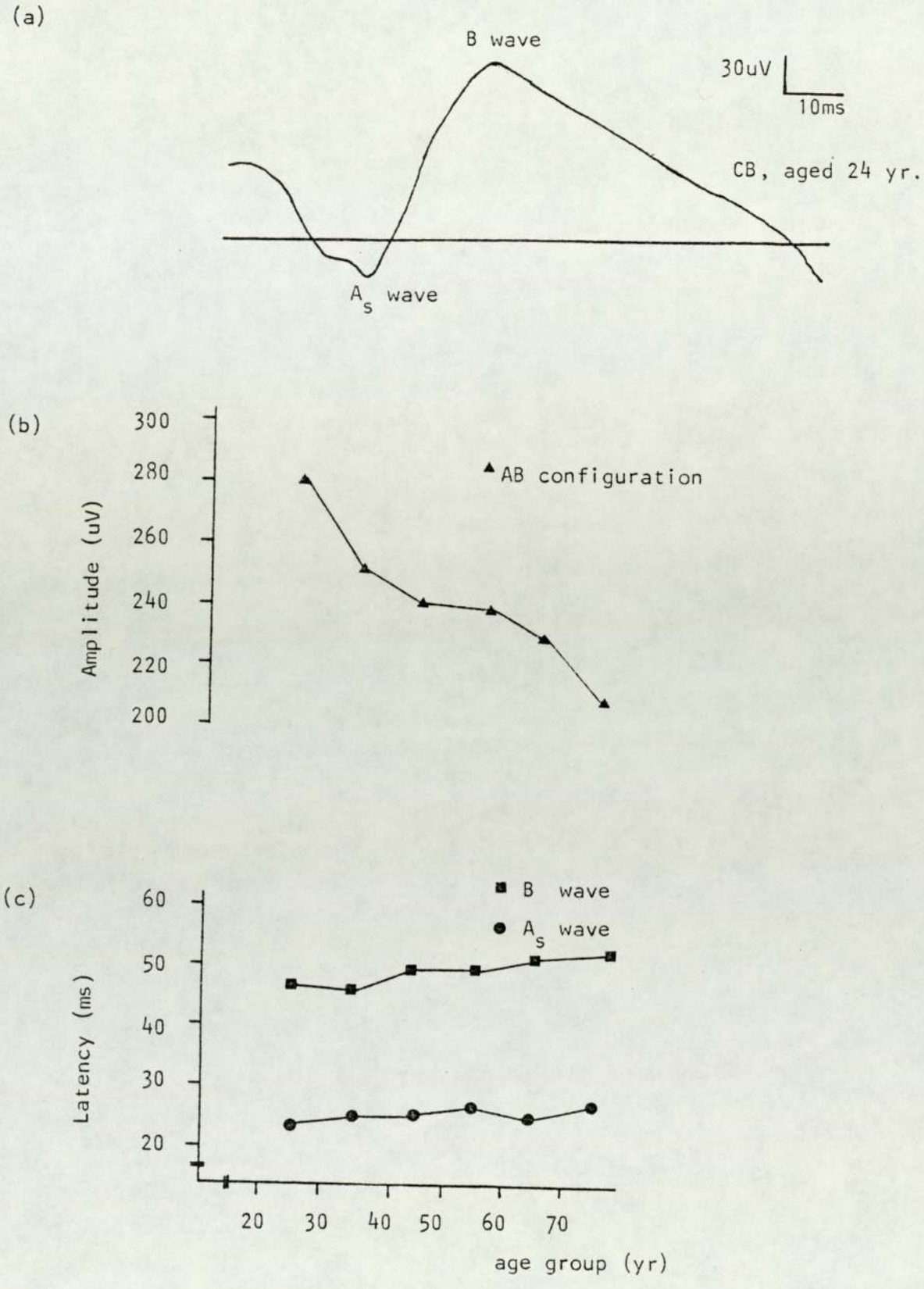


Figure 5.1

(a) Typical waveform of the dark-adapted low intensity ERG;
(b) and (c) Graphs showing the mean amplitudes of the AB configuration and the mean latencies of the A and B waves for each age group of normal subjects.
(Results are shown for right eye only).

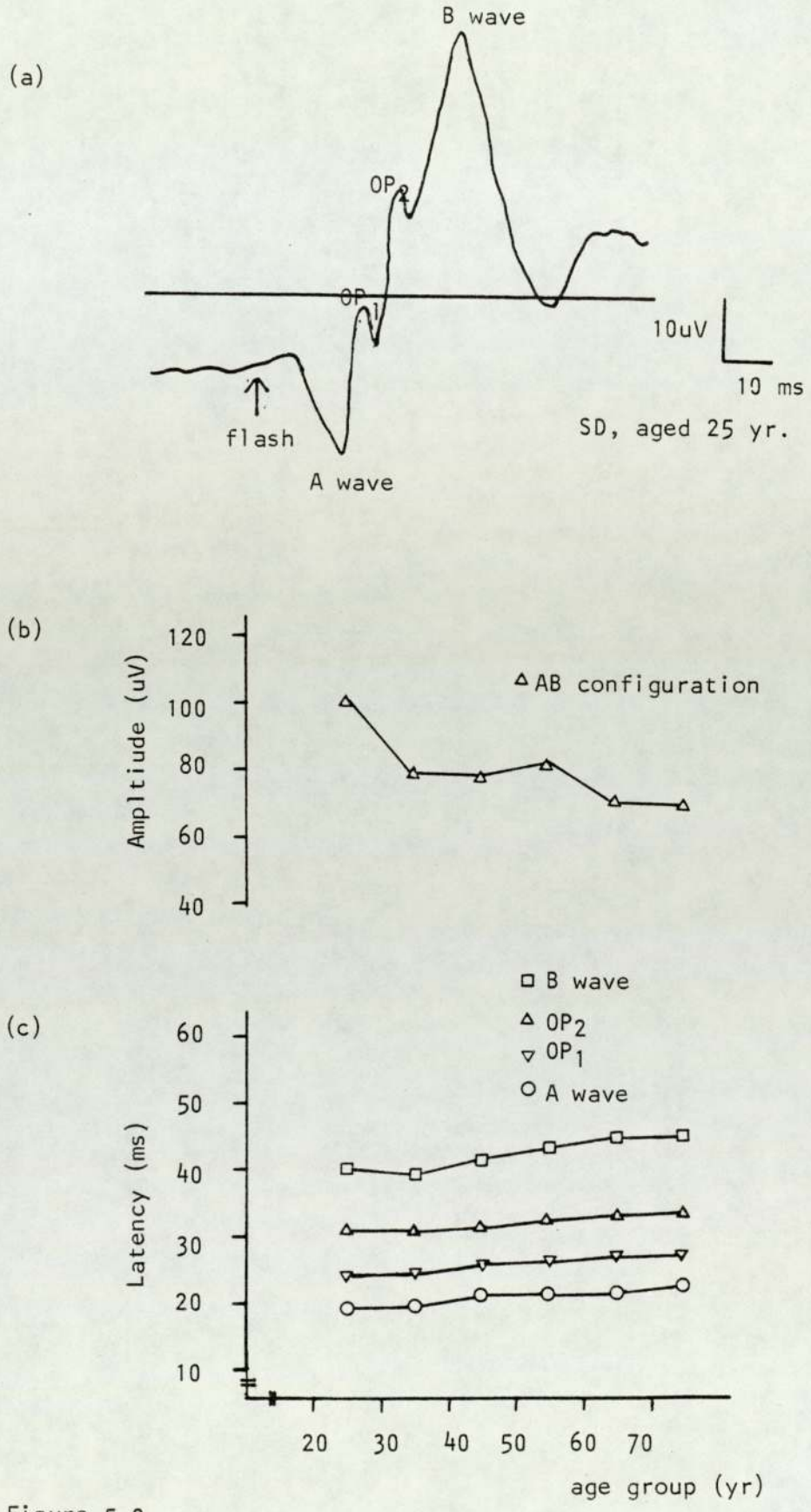


Figure 5.2

(a) Typical waveform of the photopic ERG to red stimulation;
(b) and (c) Graphs showing the mean amplitudes of the AB configuration and the mean latencies of the A and B waves and oscillatory potentials for each age group of normal subjects.
(Results are shown for the right eye only).

Age Group (year)	Males; Females	VA R L	Pupil Size R (mm) L
20-29 24.10±2.14	5 ; 5	1.183±0.024/ 1.185±0.023	4.70±0.67/ 4.70±0.67
30-39 33.50±3.10	5 ; 5	1.171±0.064/ 1.164±0.072	4.60±0.91/ 4.60±0.91
40-49 44.00±2.16	4 ; 6	1.178±0.062/ 1.178±0.062	3.65±0.67/ 3.65±0.67
50-59 54.60±3.50	6 ; 4	1.156±0.065/ 1.167±0.054	3.60±0.52 3.60±0.52
60-69 63.60±2.17	4 ; 6	1.148±0.07/ 1.125±0.10	3.40±0.74/ 3.40±0.74
70 & Over 73.90±2.85	5 ; 5	1.113±0.136/ 1.10±0.122	3.05±0.50/ 3.05±0.50

Table 5.1 Presenting the particulars of the normal subjects who participated in the study.

Age Range	DARK ADAPTED LOW INTENSITY			PHOTOPIC				
	A(ms)	B(ms)	AB(uV)	A(ms)	B(ms)	OP1(ms)	OP2(ms)	AB(uV)
20-29	24.11±1.50/ 24.86±2.24	47.86±2.38/ 46.72±2.52	281.94±43.07/ 272.0±54.52	19.34±0.84/ 19.38±0.70	40.47±2.64/ 40.14±2.85	24.25±1.42/ 24.30±1.25	31.26±0.91/ 31.36±1.16	101.74±28.72/ 97.10±33.65
30-39	25.32±1.72/ 24.86±2.37	46.86±2.57/ 48.30±2.61	250.95±47.78/ 250±93±52.23	19.60±1.53/ 19.28±0.99	39.55±2.09/ 40.46±2.91	24.38±1.28/ 24.43±1.30	30.75±1.18/ 31.31±1.38	78.20±25.26 78.69±23.19
40-49	25.26±1.54/ 24.85±1.32	49.62±4.67/ 50.65±4.34	241.29±43.84/ 243.33±44.95	20.25±0.61/ 20.00±1.26	41.13±4.26/ 42.44±3.66	25.15±1.13/ 24.33±0.98	31.55±0.82/ 31.0±0.96	76.97±12.31/ 80.65±15.17
50-59	26.23±1.80/ 26.84±1.66	49.81±2.61/ 48.98±2.54	238.61±34.04/ 239.66±33.22	20.67±0.75/ 21.42±0.97	43.16±3.47/ 44.08±2.76	26.18±0.60/ 26.0±1.10	32.63±1.04/ 32.17±0.95	81.19±12.00/ 80.42±13.19
60-69	25.81±1.58/ 26.70±1.62	51.77±2.97/ 52.93±2.85	227.88±30.24/ 224.47±33.88	21.12±0.79/ 21.30±1.04	44.38±1.63/ 43.50±1.70	26.25±1.05/ 26.1±1.14	32.58±0.98/ 32.0±1.26	70.46±15.22/ 67.69±12.56
70 & Over	27.56±2.43/ 26.48±2.44	52.78±4.68/ 53.80±3.89	209.58±36.56/ 196.33±39.55	22.38±1.80/ 22.63±1.32	45.0±2.0/ 44.80±3.17	26.50±1.31/ 26.50±1.08	32.88±1.85/ 32.40±1.65	69.87±17.75/ 67.68±15.08

Table 5.2 Giving means ± 1SD for the components of the dark-adapted and photopic ERG for each age group of normal subjects.

	Dark-Adapted Low-Intensity			Photopic				
F Value (1-way ANOVA)	A(ms)	B(ms)	AB(uV)	A(ms)	B(ms)	OP1(ms)	OP2(ms)	AB(uV)
F Value for Age Groups DF	2.89 4,45 p<0.05	10.16 4,45 p<0.01	2.70 4,45 p<0.05	6.74 4,45 p<0.01	9.26 4,45 p<0.01	6.68 4,45 p<0.01	7.10 4,45 p<0.01	5.46 4,45 p<0.01

Table 5.3 Showing the levels of significance of the components of the dark-adapted and photopic ERGs for progressive age group analysis (Results are shown for right eye only).

This could be because the photopic ERG has been recorded to red stimulation as opposed to white stimulation for the dark-adapted ERG. These results would be in general agreement with those of Martin and Heckenlively (1982) who found a significant age effect on the A and B wave amplitudes and implicit times in both sexes for their dark-adapted bright flash ERG. Out of the three types of ERGs recorded by these workers (see section 3.1), this ERG seems to be the most comparable to the dark-adapted ERG recorded in this study for which similar changes have been noted. For their photopic ERG, significant changes were reported for the A and B wave amplitudes and the B wave implicit time. In this study, a marked effect has been obtained for the A wave implicit time.

Unlike the results of Martin and Heckenlively and those of this study, Weleber (1981) did not observe any marked age changes in implicit times although he mentioned that with greater data, a small correlation might have occurred. Martin and Heckenlively attributed the discrepancy in results to the difference in the methods of analysis whereby they used three-way ANOVA and Weleber used linear regression. However, another contributing factor could be the diversity in the recording conditions of each type of ERG between laboratories, leading to varying results and hence differences in age trends.

Significant differences in the parameters of the ERG between sexes have been reported (Vainio-Mattila, 1951; Zeidler, 1959; Peterson, 1968; Martin and Heckenlively, 1982).

However, as each age group contains more or less an equal number of males and females (see Table 5.1), the effect of the sexes upon each age group is fairly constant and therefore, the age effect upon the ERG would be negligibly distorted. Nevertheless, the possible effect of the different variables upon the ERG have to be considered when comparing normal and abnormal data although the patients in this study have been age-and-sex matched with controls for statistical analysis.

The statistical analysis of the age effect on the ERG has only been performed on five age groups, that is, the 20+ to 60+ age groups as ERGs were not done on all of the subjects in the 70+ age group because of subject refusal.

Visual Evoked Responses

The typical waveformsof the VERs to flash, pattern reversal and pattern onset-offset stimulation are illustrated in Figure 5.3 The results of the various components which have been measured for each age group are presented in Tables 5.4-5.22 . The components* which have been statistically analysed as they are the most consistent in appearance, are as follows:-

* For each component, the peak latency and amplitude are given as an average of the VERs from the right and left hemispheres of each eye (see Appendix 6). Positivity is denoted by a downward deflection except for the ERG recording.

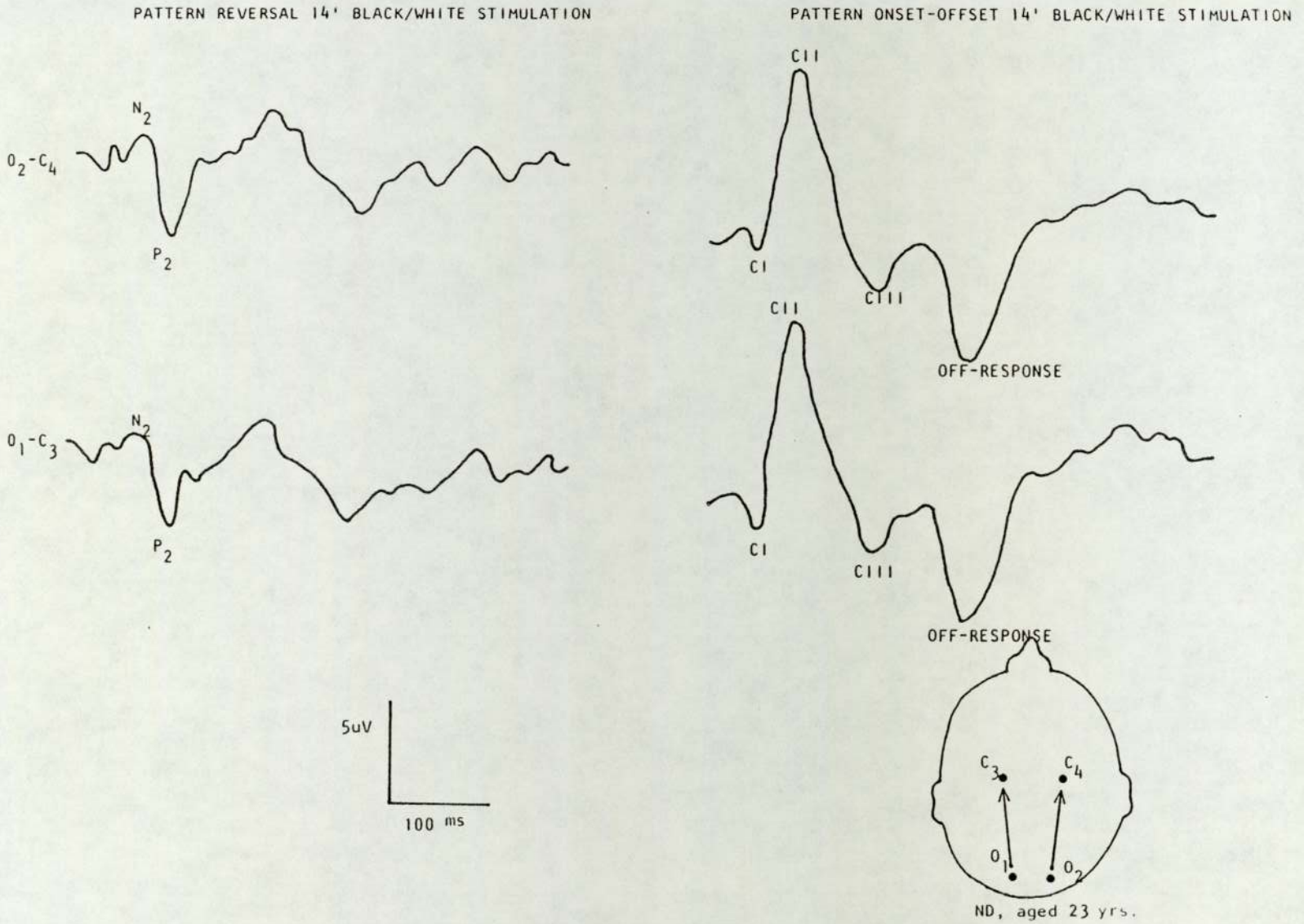


Figure 5.3 Examples of the typical waveforms seen in pattern reversal and pattern onset-offset stimulation in a normal subject (VERs are shown for right eye only). For pattern reversal stimulation the components which are identified are N2 and P2; whilst for pattern onset-offset stimulation, the components which are identified are CI, CII, CIII and the off-response

1. P_2 for flash stimulation
2. P_2 (P100) for pattern reversal stimulation
3. CII for pattern onset-offset stimulation.

Flash and Pattern Reversal Data

On inspecting the statistical results for the peak latencies of the P_2 component, a significant age effect has been demonstrated for all forms of flash and pattern reversal stimulation using two-way ANOVA ($p<0.01$; Tables 5.4-5.7). This significant ageing effect is mostly due to an increase in mean latency in the 50+ to 70+ age groups which would be in agreement with the findings of other workers for both flash and pattern reversal stimulation (Figure 5.4). (Dustman and Beck, 1969; Dustman et al. 1977; Alison et al. 1979; Stockard et al. 1979; Shaw and Cant 1980; Snyder et al. 1981; Cosi et al. 1982; Halliday et al. 1982). For pattern reversal stimulation, Halliday et al (1982) only observed this age effect in females and not in males, however the latter group generally demonstrated more delayed latencies for all age groups.

Unlike the above workers, Celesia and Daly (1977) and Sokol et al. (1981) reported a linear increase in the P100 (P_2) latency with age for pattern reversal stimulation. Sokol et al. used two check sizes (48' and 12') and found that the slope for 12' checks was nearly twice as steep as that for the 48' checks. In this study, this has not been found to be the case as the interaction variance ratio did not reach significance on comparing the results for 56'

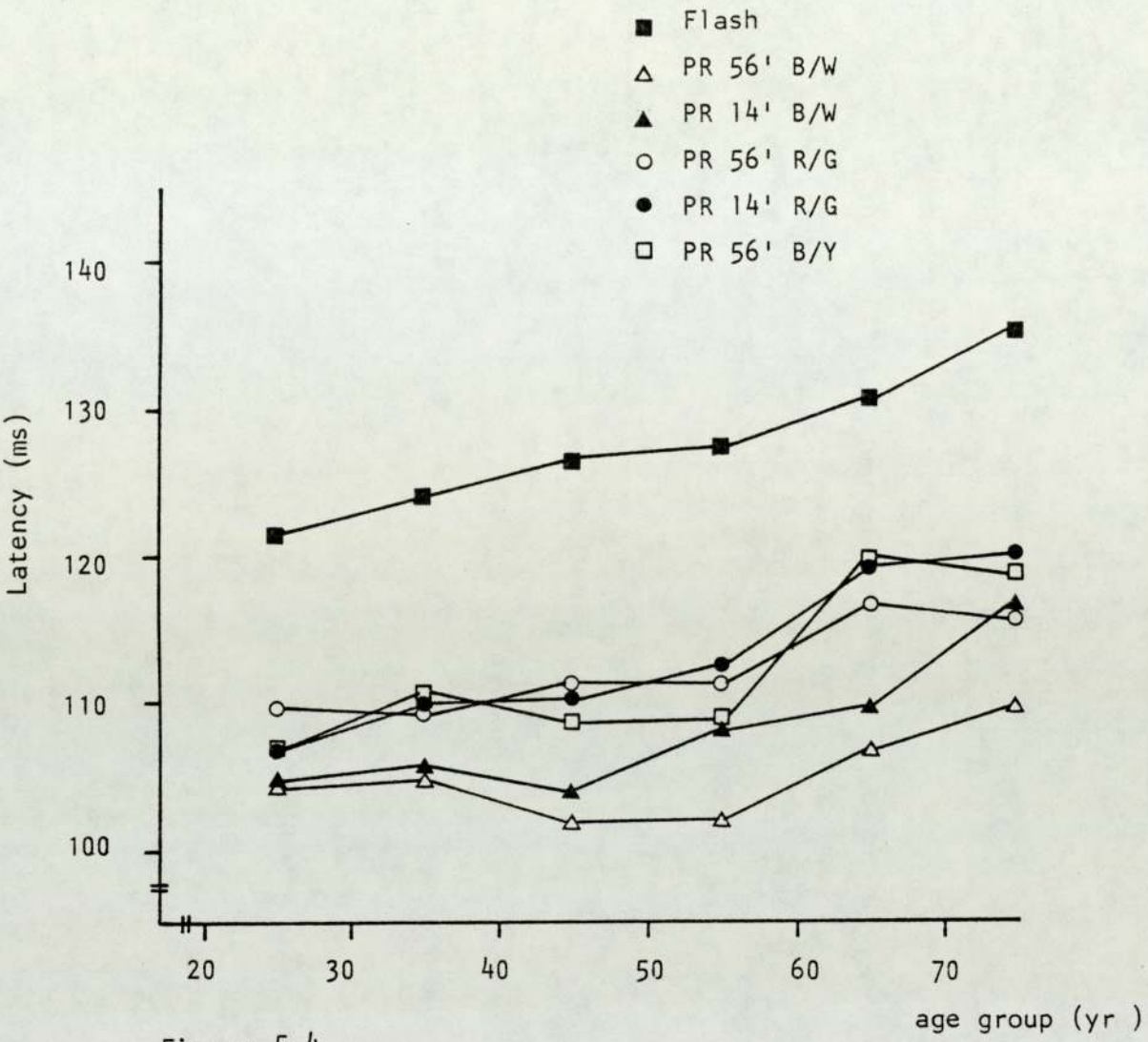


Figure 5.4

Graph showing mean latency of the P_2 component in flash and pattern reversal stimulation for each age group of normal subjects.

(Results shown for right eye only).

FLASH

Age Range		COMPONENTS			
		P1	N2	P2	N3
20-29	R	Indiscernible	72.78±13.61/	121.95±7.38/	180.38±13.38/
	L	in most cases	74.33±11.54	120.94±8.20	189.57±12.72
30-39	R	Indiscernible	82.39±12.68/	124.33±7.17/	171.36±15.92/
	L	in most cases	79.59±13.78	125.18±6.76	175.38±12.30
40-49	R	72.15±17.08/	90.25±14.13/	126.70±9.0/	181.11± 9.86/
	L	69.55±21.87	84.3±15.40	126.98±9.80	181.79±9.80
50-59	R	72.33±11.21/	93.69±8.53/	127.30±8.60/	175.20±16.17/
	L	65.29±16.59	88.97±10.99	128.38±6.85	172.25±15.96
60-69	R	72.0±6.42/	88.20±12.68/	130.98±8.58/	167.36±9.71/
	L	72.91±7.69	89.20±11.52	131.69±9.42	169.2±11.82
70 & Over	R	67.46±9.47/	91.39±10.92/	134.95±8.08/	187.41±15.25/
	L	67.23±12.34	92.72±10.85	136.0±6.83	179.27±15.57

Table 5.4 Giving the means ± 1SD for the peak latencies of the P1, N2, P2 and N3 components for flash stimulation in each age group of normal subjects

Age Range		PR 56' BLACK/WHITE		PR 56' RED/GREEN		PR 56' BLUE/YELLOW	
		COMPONENTS					
		N2	P2	N2	P2	N2	P2
20-29	R L	71.67±7.64/ 71.61±5.68	104.18±4.73/ 104.34±5.59	79.09±10.20/ 77.25±10.03	109.70±5.99/ 110.22±5.65	Indiscernible in most instances	108.68±7.55/ 109.23±7.50
30-39	R L	69.43±7.81/ 68.64±5.76	104.78±6.47/ 104.88±6.94	75.41±6.40/ 75.64±7.26	109.23±5.11/ 110.73±3.79	"	110.05±6.72/ 110.64±6.79
40-49	R L	69.14±10.36/ 69.47±10.0	101.78±4.68/ 103.90±5.78	82.64±10.49/ 87.25±9.65	111.25±4.08/ 111.83±4.77	"	108.63±5.45/ 107.68±5.74
50-59	R L	68.91±7.72/ 70.63±7.56	102.08±5.19/ 102.86±5.35	78.06±10.01/ 78.59±7.36	111.35±5.68/ 111.54±5.31	"	108.93±5.66/ 107.29±5.62
60-69	R L	75.0±6.86/ 73.50±8.72	106.90±8.59/ 108.12±7.19	83.38±9.77/ 82.0±9.66	116.55±5.23/ 115.37±5.37	78.75±10.99/ 78.75±7.50	119.75±8.59/ 118.0±8.79
70 & Over	R L	80.75±13.44/ 81.25±12.08	109.40±6.19/ 111.97±6.13	82.73±10.56/ 84.56±11.74	115.35±8.34/ 116.84±9.87		118.93±8.55/ 117.68±7.99

Table 5.5 Giving the means ± ISD for the peak latencies of the N2 and P2 components for various forms of pattern reversal stimulation in each age group of normal subjects

Age Range		PR 14' BLACK/WHITE		PR 14' RED/GREEN	
		COMPONENTS			
		N2	P2	N2	P2
20-29	R L	71.82±8.14/ 72.66±7.92	104.68±4.28/ 104.15±5.94	73.41±6.84/ 72.58±8.10	108.65±5.59/ 108.5±6.90
30-39	R L	72.59±6.71/ 70.50±6.51	105.90±4.50/ 103.05±5.67	70.65±7.57/ 68.12±8.53	109.53±4.78/ 111.43±6.31
40-49	R L	73.15±11.19/ 74.50±10.45	103.56±4.85/ 105.48±5.02	76.54±11.53/ 76.67±11.08	110.08±5.27/ 110.59±5.86
50-59	R L	78.10±8.77/ 78.0±6.214	108.13±7.65/ 107.44±8.24	78.10±7.98/ 73.5±8.81	112.63±7.90/ 111.11±6.51
60-69	R L	81.73±6.24/ 80.55±9.81	109.55±6.51/ 109.53±7.65	83.19±7.34/ 83.44±7.78	119.28±8.00/ 118.56±7.95
70 & Over	R L	80.54±7.93/ 77.50±10.90	116.58±7.08/ 117.81±7.91	83.96±12.03/ 82.21±14.62	119.85±12.12/ 119.44±12.62

Table 5.6 Giving the means ± 1SD for the peak latencies of the N2 and P2 components for various forms of pattern reversal stimulation in each age group of normal subjects

F Value	Type of Stimulus						PR 56' B/Y (1-way ANOVA)	
	Flash - PR 56' B/W		PR 56' B/W-PR 14' B/W		PR 56' R/G-PR 14' R/G			
F Value for Age Groups DF	4.43 5,54	p<0.01	5.20 5,54	p<0.01	5.34 5,54	p<0.01	5.93 4,45	p<0.01
F Value for Stimuli DF	330.91 1,54	p<0.01	16.76 1,54	p<0.01	2.47 1,54	p<0.05	N/A	
F Value for Interaction DF	1.17 5,54	NS	2.04 5,54	ns	1.09 5,54	NS	N/A	

Key: PR - Pattern Reversal; B/W - Black/White; R/G - Red /Green; B/Y - Blue/Yellow; DF - Degrees of Freedom.
NS - Not Significant.

Table 5.7 Showing the levels of significance on comparing the peak P_2 latency for two types of stimulation for progressive age group analysis. (Results are shown for right eye only).

and 14' checks for black/white and red/green stimulation respectively (Table 5.7). On examining Figure 5.4, it can be seen that the divergence of the curves for 56' and 14' does not become evident until the 50+ age group which could account for the difference in the results, as Sokol et al fitted regression lines to their data. The effect of decreasing pupillary diameter with increasing age is not completely responsible for the increase in latency of the P_2 component. On inspecting Table 5.1, it can be seen that the difference in the mean pupillary diameters for the 20+ and 70+ age groups is 1.65 mm (4.7 - 3.05). This would result in a 0.35 log unit decrease in retinal illuminance which would lead to an increase in latency of about 5.25 ms for both 56' and 14' checks. Although this amount seems to greatly account for the mean increase in latency seen for the 56' checks (5.32 ms), it is certainly not large enough to account for the increase seen for the 14' checks (11.90 ms). If the difference in mean pupillary diameters is taken between the 40+ age group instead (where no noticeable age changes are noted) and the 70+ age group, then the difference would only be 0.6 mm. Whilst the differnce in the mean P_2 latency for 56' and 14' checks is 7.62 and 13.02 ms respectively.

A marked difference has been obtained between the mean latencies for pattern reversal 56' and 14' checks for black/white ($p<0.01$) and red/green ($p<0.05$) responses respectively. (Table 5.7). It has also been observed that the mean latencies of the responses to coloured stimulation (red/green; blue/yellow) are more delayed than those to black/white stimulation for identical check sizes which

was also noted by Dixon (1981). However, this does not seem to follow any special trends with age (Table 5.8). The average difference between the mean latencies for 56' black/white and 56' red/green stimulation is 7.4 ms and for 14' checks it is 5.5 ms. It has been stated that a one log unit decrease in retinal illuminance results in an increase in latency of approximately 15 ms (Halliday, 1977). The general luminance of the red/green checks is about one-third of the value for the black/white checks (Dixon, 1981 also found a similar difference in general luminance so as to obtain chromatically balanced contrast) which is equivalent to about 0.3 log units and hence would lead to a change in latency of approximately 5 ms (see appendix 2). Although the decrease in general luminance for the red/green checks might largely account for the more delayed mean latencies for red/green stimulation it is possible that neural processing for chromatic contrast takes longer than for black/white contrast.

The amplitudes of the N_2P_2 configuration for flash and pattern reversal stimulation have failed to demonstrate any significance with increasing age for the age span studied (Table 5.9-5.12; Figure 5.5). These results would not be in agreement with those of Dustman and Beck (1969) and Dustman et al (1977) for flash stimulation whereby they found an increase in amplitude of the earlier waves (I - IV, which therefore include N_2 and P_2) with age and those of Cosi et al. (1982), who found an increase in amplitude of all the waves for the older age groups (>60 yr). On the otherhand, Copenhaver and Perry (1964) reported a decrease in amplitude with increasing age. This variation

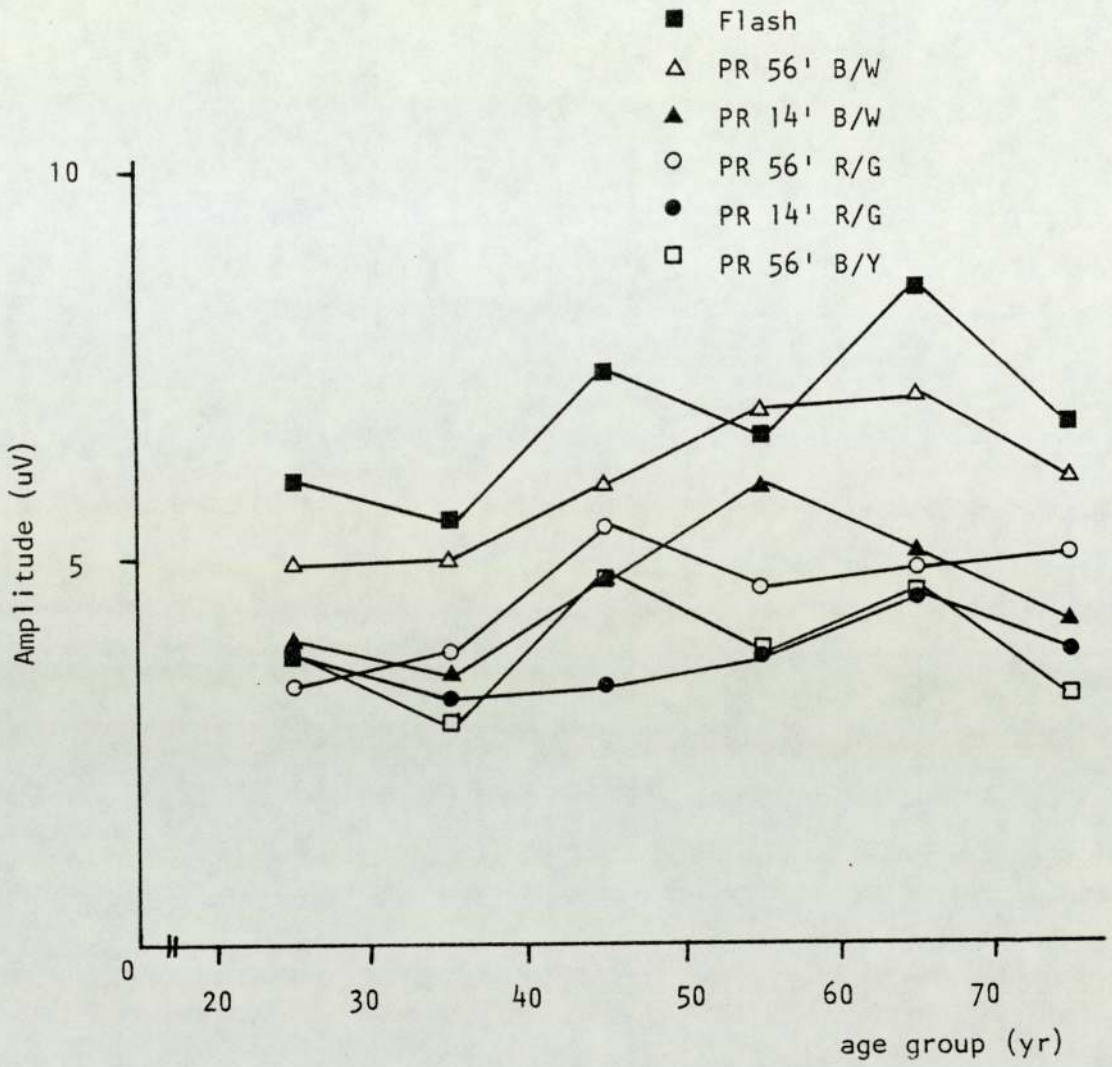


Figure 5.5

Graph showing mean amplitude of the N_2P_2 configuration in flash and pattern reversal stimulation for each age group of normal subjects.

(Results are shown for right eye only).

Age Range	PATTERN REVERSAL			PATTERN ONSET-OFFSET		
	56'	56'	14'	56'	56'	14'
	R/G - B/W	B/Y - B/W	R/G - B/W	R/G - B/W	B/Y - B/W	R/G - B/W
20 - 29	5.525	4.505	3.975	21.225	29.18	12.925
30 - 39	4.45	5.275	3.625	17.125	35.105	8.725
40 - 49	9.475	6.855	7.50	17.80	37.725	5.725
50 - 59	9.275	6.855	4.55	20.80	39.30	10.325
60 - 69	9.65	12.85	9.725	12.95	38.475	17.525
70 & Over	5.95	9.53	3.375	28.275	48.055	23.675
$\bar{x}$	7.39	7.645	5.46	19.70	37.97	13.15

Key: B/W - Black/White; R/G - Red/Green; B/Y - Blue/Yellow

Table 5.8 Giving differences between mean latencies for black/white and coloured stimulation for identical check sizes.

FLASH

Age Range		COMPONENTS		
		P_1N_2	N_2P_2	P_2N_3
20-29	R L		5.90±3.51/ 6.03±3.06	7.24±3.17/ 6.23±2.93
30-39	R L		5.50±3.62/ 6.44±3.41	4.64±1.757/ 5.05±1.62
40-49	R L	4.93±5.34/ 4.51±4.15	7.39±4.63/ 7.85±3.94	9.17±4.64/ 8.52±4.54
50-59	R L	5.82±4.93/ 5.21±3.36	6.56±4.57/ 7.03±5.27	6.93±4.42/ 6.69±3.95
60-69	R L	6.06±4.51/ 5.54±5.53	8.52±5.71/ 8.95±6.01	8.99±5.45/ 7.38±4.68
70 & Over	R L	3.49±1.83/ 3.03±1.74	6.70±3.12/ 7.89±4.17	6.57±2.99/ 7.75±4.75

Table 5.9 Giving the means ± 1SD of the amplitudes of the P1 N2, N2 P2 and P2 N3 configurations for flash stimulation in each age group of normal subjects

Age Range		PR 56' BLACK/WHITE	PR 56' RED/GREEN	PR 56' BLUE/YELLOW
		COMPONENTS		
		N_2P_2	N_2P_2	N_2P_2
20-29	R L	4.90±1.67/ 4.52±1.88	3.23±1.73/ 3.39±1.91	3.75±1.02/ 3.10±1.03
30-39	R L	4.99±2.07/ 4.57±1.39	3.77±1.17/ 4.04±1.23	2.84±1.14/ 2.71±1.06
40-49	R L	5.94±2.43/ 6.41±2.81	5.37±2.38/ 4.74±1.88	4.66±1.43/ 5.36±1.67
50-59	R L	6.94±3.44/ 6.23±3.14	4.72±2.42/ 4.42±2.29	3.69±1.34/ 3.55±1.54
60-69	R L	7.02±5.76/ 7.31±7.60	4.81±2.95/ 4.91±3.31	4.49±3.81/ 4.20±2.82
70-79	R L	6.00±1.92/ 6.45±2.60	5.04±1.74/ 5.22±2.34	3.20±1.92/ 3.79±1.57

Table 5.10 Giving the mean ± 1SD of the amplitudes of the N2 P2 configuration for various forms of pattern reversal stimulation in each group of normal subjects

Age Range		PR 14' BLACK/WHITE	PR 14' RED/GREEN
		COMPONENTS	
		N_2P_2	N_2P_2
20-29	R	3.90±1.09/	3.75±1.31/
	L	4.02±1.0	3.71±1.11
30-39	R	3.44±1.37/	3.15±0.89/
	L	3.38±1.78	3.06±0.86
40-49	R	4.70±1.98/	3.36±1.13/
	L	4.49±2.09	4.30±1.94
50.59	R	5.96±2.12/	3.72±2.0/
	L	5.29±1.95	3.57±2.24
60-69	R	5.12±3.57/	4.44±3.05/
	L	4.89±4.64	3.87±3.30
70 & Over	R	4.18±2.11/	3.75±2.19/
	L	4.50±2.06	4.06±2.54

Table 5.11 Giving the means ± 1SD for the amplitudes of the N2-P2 configuration for various forms of pattern reversal stimulation in each age group of normal subjects

	Type of Stimulus			
F Value	Flash - PR 56' B/W	PR 56' B/W-PR 14' B/W	PR 56' R/G - PR 14'R/G	PR 56' B/Y (1-way ANOVA)
F Value for Age Groups DF	1.13 5,54 NS	1.41 5,54 NS	0.79 5,54 NS	0.89 4,45 NS
F Value for Stimuli DF	2.00×10^{-3} 1,54 NS	25.23 1,54 $p < 0.01$	11.61 1,54 $p < 0.01$	N/A
F Value for Ineraction DF	0.38 5,54 NS	0.58 5,54 NS	0.25 5,54 NS	N/A

Table 5.12 Showing the levels of significance on comparing the N_2P_2 configuration for two types of stimulation for progressive age group analysis. (Results are shown for right eye only).

in the results could be partly due to different conditions of stimulation for example, flash rate, intensity, etc.

As already mentioned, there is no marked change in the amplitude of the N_2P_2 configuration with age for the pattern reversal responses. This finding is supported by those of Celesia and Daly (1977), Snyder et al. (1981 - if the preadolescence data is disregarded) and Halliday et al. (1982). Shaw and Cant (1981) fitted their data to a third order polynomial regression function but on inspecting their data for the post adolescence period to old age, the amplitude of the P100 component does not seem to markedly vary. However, in this study, it has been found that the amplitudes for the 56' responses are significantly larger than those for the 14' responses for both black/white and red/green stimulation (Table 5.12).

The P_2 component has been accepted as being the most repeatable and least variable component for flash and pattern reversal stimulation. In this study, it has been found to be present in the large majority of responses for both forms of stimulation (only three clinically normal patients in the 70+ age group failed to reveal discernible responses to blue/yellow stimulation). For flash stimulation it is seen from Table 5.4, that the standard deviations for P_1, N_2 and N_3 are larger than those for P_2. These components are identifiable in both eyes (and in both hemispheres for each eye) in the following percentages (expressed as a percentage of the total population of normal subjects):- P_1 - 50%; N_2 - 96.7%; P_2 - 100%; N_3 - 83.3%.

For pattern reversal stimulation, the P_2 component for blue/yellow stimulation is more rounded and broader than that for black/white and red/green stimulation, therefore making its peak latency more difficult to specify (Figure 5.6). The N_2 component is seen to be flattened in many of the responses. The percentage appearance of the N_2 component for black/white, red/green and blue/yellow stimulation respectively, is as follows for 56' checks: 83.3%, 83.3% and 45.5%.

Due to the absence of discernible responses in three subjects in the 70+ age group for both pattern reversal and pattern onset-offset stimulation the responses of this group have not been included in the statistical analysis as the ANOVA program requires an equal number of subjects in each group and it was felt that any age changes should already be manifest in the 50+ and 60+ age groups.

Pattern Onset-Offset Data

Like the P_2 component of the pattern reversal response, the CII component of the pattern onset response does not reveal a marked increase in latency until the fifth decade. A significant age effect was obtained for all forms of stimulation ($p < 0.01$) except for 56' blue/yellow stimulation (Table 5.13-5.18; Figure 5.7). The lack of significance for blue/yellow stimulation could be partly because of the omission of the 70+ age group from the statistical analysis, however, it could also be attributed to the large increase in variance in the results for the older age groups, that is, the 60+ age group. (This increase in variance has also been seen for

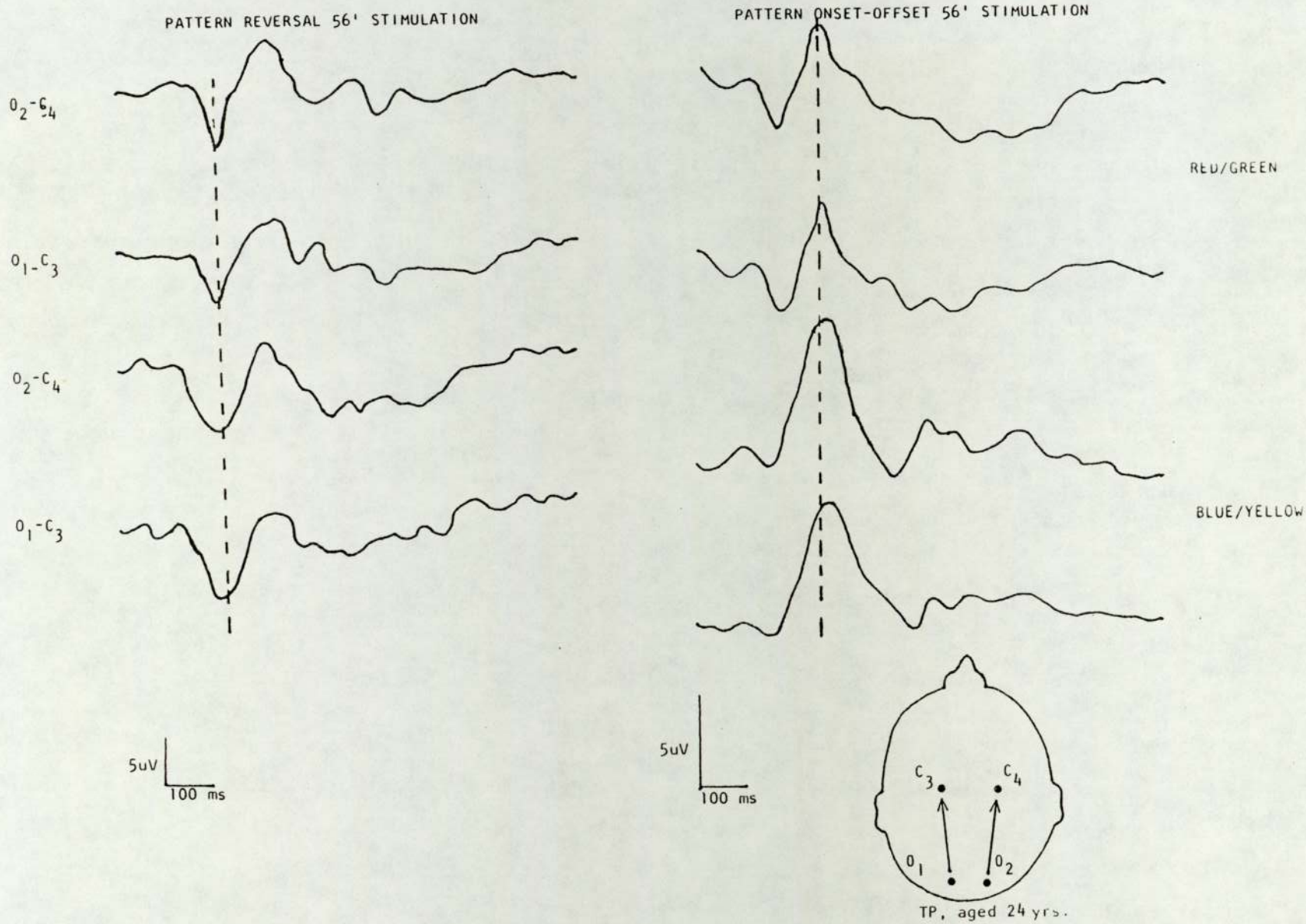


Figure 5.6 Examples of the "roundedness" of the blue/yellow responses for both pattern reversal and onset-offset stimulation in comparison to the red/green responses

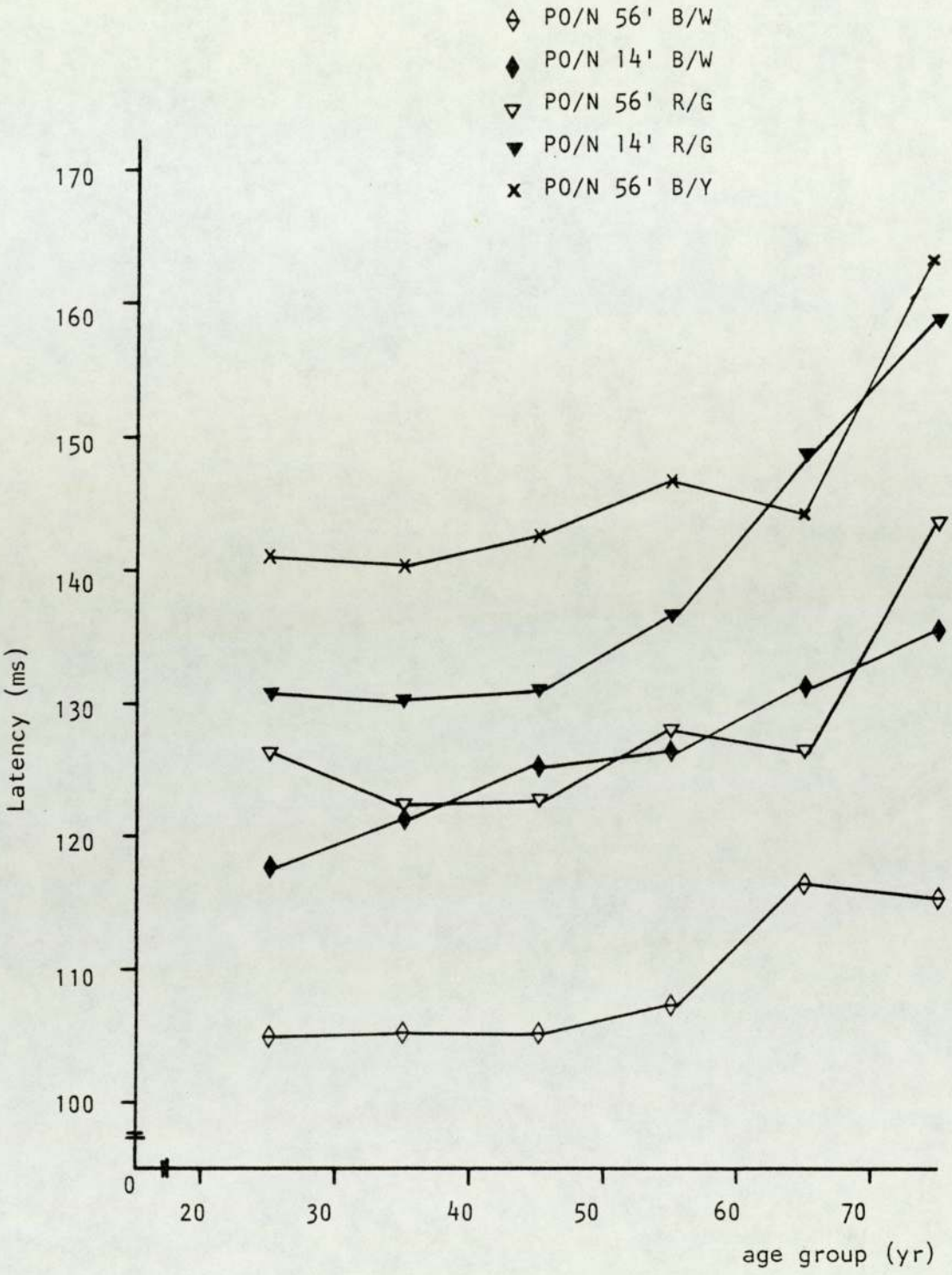


Figure 5.7

Graph showing mean latency of the CII component in pattern onset-offset stimulation for each age group of normal subjects.

(Results are shown for right eye only).

P(O-N) 56' BLACK/WHITE

Age Range		COMPONENTS			
		CI	CII	CIII	OFF
20-29	R	75.28±8.02/	105.08±8.36/	145.41±9.84/	240.3±21.58/
	L	74.61±11.36	104.15±7.74	140.97±9.42	239.82±23.30
30-39	R	70.78±8.78/	105.08±10.45	149.58±16.38/	245.94±20.23/
	L	70.16±7.37	104.06±8.62	146.25±15.90	245.90±21.23
40-49	R	70.76±8.64/	105.08±8.73/	145.60±11.08/	248.58±12.69/
	L	72.58±5.83	103.23±7.94	145.85±11.43	248.97±10.23
50-59	R	70.03±5.18/	107.20±8.39/	151.93±17.46	247.92±14.37/
	L	70.64±6.03	105.36±6.86	155.41±17.03	244.11±14.93
60-69	R	73.53±8.84/	116.48±13.41/	175.15±17.46/	258.58±21.52/
	L	74.14±8.66	115.0±12.79	167.84±16.70	259.28±18.63
70 & Over	R	74.11±7.06/	115.28±8.56/	175.15±20.09/	257.31±21.38/
	L	72.42±6.154	115.05±9.87	178.69±20.0	250.50±18.16

Table 5.13 Giving the means ± 1SD for the peak latencies of the CI, CII, CIII and "OFF" components for black/white 56' pattern onset-offset stimulation in each age group of normal subjects

P(O-N) 56' RED/GREEN

Age Range		COMPONENTS			
		CI	CII	CIII	OFF
20-29	R	88.64±13.05/	126.30±6.44/	160.71±14.34/	260.95±15.15/
	L	86.21±12.72	123.63±6.72	162.33±14.83	264.44±18.62
30-39	R	81.68±9.71/	122.20±10.03/	165.29±16.05/	256.88±16.89/
	L	82.18±10.49	121.71± 9.58	163.86±16.45	252.29±22.75
40-49	R	87.65±8.06/	122.80±7.58/	157.50±11.18/	258.75±12.28/
	L	87.31±7.99	122.64±6.67	161.75±8.17	258.56±12.60
50-59	R	89.29±9.47/	128.0±9.03/	161.19±15.44/	258.92±12.57/
	L	90.04±11.03	130.47±8.64	168.14±16.60	260.33±12.78
60-69	R	95.76±8.42/	126.53±7.28/	178.36±24.81/	260.33±14.66/
	L	97.56±7.42	127.14±9.20	175.20±27.25	262.86±12.26
70 & Over	R	98.06±10.80/	143.55±14.09/	183.29±15.20/	263.80±12.40/
	L	100.11±10.17	145.83±13.79	182.67±19.37	267.64±10.51

Table 5.14 Giving the means ± 1SD for the peak latencies of the CI, CII,CIII and "OFF" components for red/green 56' pattern onset-offset stimulation in each age group of normal subjects

P(O-N) 56' BLUE/YELLOW

Age Range		COMPONENTS			
		CI	CII	CIII	OFF
20-29	R L	86.75±8.14/ 89.84±8.34	141.18±7.57/ 141.28±8.41	183.54±15.95/ 196.63±14.07	271.85±12.04/ 273.15±16.64
30-39	R L	88.54±9.50/ 88.77±12.57	140.18±7.48/ 138.82±7.65	195.20±22.11/ 191.40±16.56	289.05±29.93/ 299.94±30.88
40-49	R L	89.93±9.93/ 86.50±12.34	142.80±6.40/ 137.39±6.64	214.31±11.58/ 198.80±15.21	278.71±28.85/ 281.15±29.12
50-59	R L	92.42±10.60/ 92.32±13.24	146.50±10.48/ 143.66±11.26	202.28±29.50/ 211.72±31.07	279.11±29.55/ 271.96±25.57
60-69	R L	106.79±15.35/ 104.38±19.49	144.95±16.98/ 147.13±17.92	209.17±34.08/ 204.38±27.19	287.92±35.34/ 288.39±28.39
70 & Over	R L	107.95±19.42/ 105.63±18.06	163.33±17.34/ 166.04±17.99	206.0±30.58/ 200.94±21.79	279.06±41.70/ 288.33±38.39

Table 5.15 Giving the means ± 1SD for the peak latencies of the CI, CII, CIII and "OFF" components for blue/yellow 56' pattern onset-offset stimulation in each age group of normal subjects

P(O-N) 14' BLACK/WHITE

Age Range		COMPONENTS			
		CI	CII	CIII	OFF
20-29	R L	79.92±9.67/ 80.05±9.97	117.89±9.03/ 116.76±10.12	156.42±16.13/ 153.07±18.03	263.28±26.70/ 256.50±21.93
30-39	R L	85.32±9.79/ 83.33±11.76	121.45±9.72/ 120.63±7.79	158.79±11.55/ 157.25±18.24	263.67±14.10/ 266.10±10.50
40-49	R L	76.59±9.98/ 78.06±8.23	125.33±7.21/ 122.95±7.02	161.21±15.15/ 161.43±14.52	259.28±14.11/ 254.43±16.75
50-59	R L	81.88±13.10/ 78.97±11.77	126.60±10.93/ 123.56±1.59	170.22±21.84/ 161.42±23.59	261.11±20.64/ 210.04±19.41
60-69	R L	88.0± 7.69/ 90.53±7.95	131.33±12.68/ 134.17±12.16	192.58±23.46/ 193.79±25.40	266.43±9.45/ 253.80±13.59
70 & Over	R L	87.89±9.673/ 90.79±10.82	135.05±13.14/ 136.75±14.96	189.81±24.13/ 185.21±25.34	250.92±17.44/ 251.46±25.34

Table 5.16 Giving the means ± ISD for the peak latencies of the CI, CII, CIII and "OFF" components for black/white 14' pattern onset-offset stimulation in each age group of normal subjects

P (O-N) 14' RED/GREEN

Age Range		COMPONENTS			
		CI	CII	CIII	OFF
20-29	R L	78.40±12.93/ 79.15±12.19	130.80±8.64/ 128.10±7.90	181.41±16.42/ 176.18±16.49	276.95±18.37/ 284.17±14.46
30-39	R L	85.93±14.15/ 87.0±13.08	130.18±10.20/ 124,29±10.60	183.21±14.03/ 176.28±14.23	264.69±17.75/ 258.86±11.38
40-49	R L	86.11±11.26/ 86.00±9.79	131.05±9.34/ 130.97±9.13	187.73±15.49/ 180.75±14.47	264.43±17.71/ 262.54±15.38
50-59	R L	85.64±8.19/ 91.68±8.78	136.93±8.98/ 138.79±9.02	175.42±22.2/ 178.4±23.64	278.17±19.95/ 272.70±22.54
60-69	R L	99.37±10.63/ 102.39±11.95	148.85±12.75/ 151.25±12.81	195.50±17.52/ 202.50±20.61	280.12±18.09/ 273.43±10.97
70 & Over	R L	97.0±15.90/ 105,5±17.85	158.73±15.94/ 157.28±13.36	203.63±15.35/ 209.25±11.95	268.0±22.74/ 275.83±23.50

Table 5.17 Giving the means ± 1SD for the peak latencies of the CI, CII, CIII and "off" components for pattern onset-offset 14' red/green stimulation in each age group of normal subjects

F Value	Type of Stimulus						PO/N 56' B/Y (1-way ANOVA)	
	Flash - PO/N 56' B/W		PO/N 56' B/W - PO/N 14' B/W		PO/N 56' R/G - PO/N 14' R/G			
F Value for Age Groups	5.01		3.61		11.57		0.47	
DF	5,54	p<0.01	5,54	p<0.01	5,54	p<0.01	4,45	NS
F Value for Stimuli	134.72		86.72		86.77		N/A	
DF	1,54	p<0.01	1,54	p<0.01	1,54	p<0.01		
F Value for Interaction	0.42		0.45		3.83		N/A	
DF	5,54	NS	5,54	NS	5,54	p<0.01		

Key:- PO/N - Pattern onset/offset; B/W - Black/white; R/G - Red/Green; B/Y - Blue/Yellow

Table 5.18 Showing the levels of significance on comparing the peak CII latency for two types of stimulation for progressive age group analysis (results are shown for right eye only).

pattern reversal stimulation but to a lesser extent (Table 5.5) This increase in variance and the absence of discernible responses in the older age groups are possibly more due to 1) the greater lens absorption of mainly the blue wavelengths as the yellow lens pigment accumulates, as well as 2) the retinal changes which occur at this age.

Similar to the P_2 component of pattern reversal stimulation, the effect of decreasing pupillary diameter with increasing age does not completely account for the increase in latency of the CII component, especially for the 14' check size. The decrease in retinal illuminance of 0.35 log units due to the reduction in mean pupillary diameter between the 20+ and 70+ age groups, would cause an increase in latency of approximately 10.5 ms. Once more, this amount may largely appear to account for the mean increase in latency seen for the 56' checks (10.20 ms - although this would not seem to be the case if the mean pupillary diameter is compared between the 40+ and 70+ age group, whereby there is only 0.6 mm difference but the mean difference in latency remains at 10.20 ms), but it does not sufficiently account for the 14' checks (17.18 ms).

In addition to the age effects, a significant difference has also been obtained between the mean latencies for 56' and 14' checks for black/white and red/green combinations respectively, ($p<0.01$; Table 5.18). On a whole, the differences between the mean latencies for 56' and 14' checks for pattern onset stimulation are larger than those for pattern reversal stimulation for all age groups (Figure 5.5, 5.7). It has also been observed that the differences in

mean latencies between black/white and coloured responses for the same check size are much greater than those for pattern reversal stimulation (Table 5.8). The greatest difference is seen between blue/yellow and black/white 56' stimulation. This is because the pattern onset response to blue/yellow is so much later than the other responses which is probably due to the coarser nature of the blue mechanism in comparison to the red/green mechanism, leading to a longer integration time (Brindley, 1970; Estevez et al. 1975; Taylor, 1983).

Once more, it is thought that the difference in mean latency between black/white and coloured stimulation might not be totally accounted for by the decrease in general luminance. It has been reported that for the CII component, there is an increase in peak latency of about 30 ms per log unit (van der Tweel et al. 1979; Spekreijse, 1980). Therefore the decrease in luminance for say, 56' red/green should result in an increase in latency of approximately 10 ms. This is in comparison to 19.7 ms obtained between the red/green and black/white responses (Table 5.8).

The differences between the pattern onset and pattern reversal results which have been mentioned in the previous paragraphs, lend support to Spekreijse's (1980) comment that these two forms of stimulation are of a different nature.

There is no significant change in the amplitude of the CI CII configuration with increasing age for either black/white or coloured

stimulation (Table 5.19-5.22 Fig.5.8) and there is also no marked difference between the size of the response for 56' and 14' checks for each stimulus (Table 5.22).

As there have been relatively few studies presented on the normative data for pattern onset-offset stimulation, the results obtained in this study will be further discussed. From Tables 5.5-5.7; 5.13-5.17, it can be seen that the standard deviations for the CII contour-specific component of the pattern onset responses are generally larger than those for the P_2 component of pattern reversal. This also applies for the other components of onset-offset stimulation (CI, CIII and the off-response) in pattern onset-offset (Table 5.13-5.17). It has been found that CII* is the most consistent and repeatable component (see appendix 7) although the results of two clinically normal subjects (29 and 30 years old respectively) have been excluded from the normative data as they both demonstrate a major negative component not occurring until about 140 and 170 ms respectively for 56' black/white stimulation with the other components being similarly affected.

* With the exception of the two subjects whose data has been excluded from the study, it has been observed that for 56' black/white stimulation, the latencies of the CII component fall between 94 ms and 125 ms for the 20-29 age group. This is the approximate range of latency values up to the 50-59 age group. For the two older age groups (over 60 yrs) the latencies range from 102-139 ms, with more subjects starting to give values around 120 - 130 ms in comparison to the younger age groups.

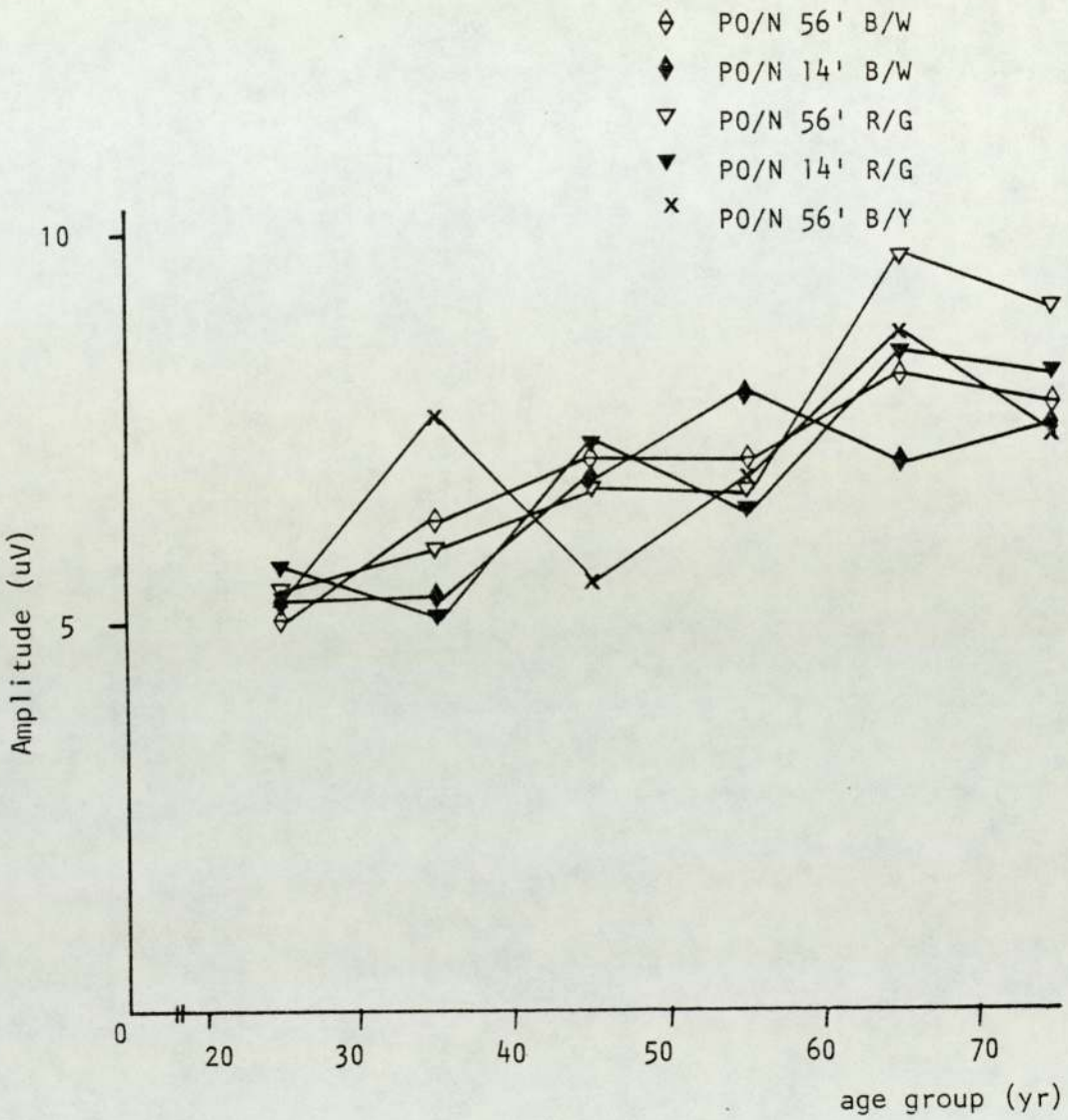


Figure 5.8

Graph showing mean amplitude of the CICII configuration in pattern onset-offset stimulation for each age group of normal subjects.

(Results are shown for right eye only).

Age Range		P(O-N) 56' BLACK/WHITE			P(O-N) 56' RED/GREEN		
		COMPONENTS					
		C1 C11	C11 C111	OFF	C1 C11	C11 C111	OFF
20 - 29	R	3.52±1.49/	5.11±1.46/	2.67±1.08/	4.22±2.06/	5,29±1.84/	3.41±0.85/
	L	3.10±1.49	4.78±1.13	3.94±1.09	3.94±1.45	4.77±1.45	3.94±0.89
30 - 39	R	5.90±2.74/	6.30±2.75/	3.83±1.65/	5.52±3.77/	5.95±2.75/	3.80±2.0/
	L	5.98±3.66	6.13±2.15	3.72±2.16	6.38±3.66	5.98±2.76	4.60±1.89
40 - 49	R	7.90±4.81/	7.17±5.07/	5,62 ±2.75/	5.57±2.20/	6.86±4.74/	3.67±1.25/
	L	6.60±4.05	6.73±4.03	5.45±2.37	6.94±2.45	6.77±3.24	3.60±1.17
50 - 59	R	8.25±4.82/	7.11±3.62/	4.38±1.94/	7.78±5.71/	6.76±3.11/	3.99±2.03/
	L	7.54±4.58	6.47±4.23	4.33±2.15	8.46±6.92	5.80±3.54	3.18±1.41
60 - 69	R	11.80±9.65/	8.21±4.83/	6.54±1.94/	8.74±3.79/	9.79±4.99/	6.86±3.14/
	L	12.23±9.92	10.29±5.56	8.14±2.15	7.95±4.80	9.55±4.36	8.14±2.69
70 & Over	R	9.98±4.08/	7.83±2.14/	3.35±1.80/	11.28±4.08/	9.18±4.18/	7.00±5.75/
	L	11.91±4.61	9.53±4.61	4.50±2.80	10.58±6.46	10.45±4.54	4.78±3.28

Table 5.19 Giving the means ± 1SD for the amplitudes of the C1C11, C11C111 configurations and the off-response for various forms of pattern onset-offset stimulation in each age group of normal subjects

P (O-N) 56' BLUE/YELLOW

Age Range		COMPONENTS		
		CI CII	CII CIII	OFF
20 - 29	R	5.43±1.85/	5.12±3.12/	4.82±1.48/
	L	5.03±2.31	6.27±3.99	3.35±1.00
30 - 39	R	7.25±6.83/	7.71±6.61/	2.96±1.06/
	L	5.93±3.79	6.01±4.30	4.91±3.64
40 - 49	R	5.87±1.51/	5.50±1.93/	3.48±1.33/
	L	5.60±1.86	5.67±2.60	3.90±1.14
50 - 59	R	8.10±5.52/	6.75±5.66/	3.50±1.69/
	L	7.71±5.45	6.27±4.05	3.71±1.51
60 - 69	R	12.40±7.56/	8.77±6.60/	6.47±2.62/
	L	8.01±4.12	8.39±6.93	7.92±5.07
70 & Over	R	11.03±6.63/	7.49±3.31/	5.69±2.65/
	L	7.66±4.59	7.13±3.56	6.55±4.47

Table 5.20 Giving the means ± 1SD for the amplitudes of the CI CII and CII CIII configurations and "OFF" response for blue/yellow 56' pattern onset-offset stimulation in each age group of normal subjects

Age Range		P(O-N) 14' BLACK/WHITE			P(O-N) 14' RED/GREEN		
		COMPONENTS					
		CI CII	CII CIII	OFF	CI CII	CII CIII	OFF
20 - 29	R	3.78±1.41/	5.11±1.46/	3.78±1.30/	6.13±2.15/	5.83±2.97/	4.18±1.75/
	L	4.14±1.60	5.50±2.17	3.23±1.09	5.95±2.03	5.43±2.93	4.42±1.10
30 - 39	R	4.66±3.025/	5.23±1.64/	4.15±1.40/	5.13±2.91/	5.13±3.36/	3.29±1.82/
	L	4.81±3.71	5.63±2.99	4.19±2.10	5.13±3.49	4.87±3.50	3.02±1.80
40 - 49	R	7.71±5.92/	7.06±2.87/	4.47±2.81/	8.56±4.41/	7.34±5.27/	5.12±1.23/
	L	7.72±5.40	5.37±3.40	4.92±2.27	7.66±2.73	8.32±4.99	3.77±1.06
50 - 59	R	9.95±8.24/	7.95±3.72/	4.58±3.57/	8.20±4.91/	6.41±3.38/	6.44±3.90/
	L	10.30±7.74	7.10±3.40	4.57±2.72	8.86±6.36	5.16±3.51	7.02±4.02
60 - 69	R	10.35±4.80/	7.10±3.22/	3.71±2.20/	9.64±4.48/	8.41±2.89/	6.25±8.61/
	L	10.55±5.50	7.70±3.89	4.13 ±2.02	10.03±6.62	5.78±3.52	9.80±9.57
70 and over	R	9.99±10.41/	7.54±6.55/	3.90±2.447	10.24±10.96/	8.20±4.46/	5.46±4.38/
	L	9.84±10.84	6.41±4.67	4.38±3.84	10.13±11.93	9.46±4.33	5.51±3.98

Table 5.21 Giving the means ± 1SD for the amplitudes of the CI CII and CII CIII configurations and "OFF" response for various forms of pattern onset-offset stimulation in each age group of normal subjects

	Type of Stimulus							
F Value	Flash -PO/N 56' B/W		PO/N56'B/W -PO/N14'B/W		PO/N56'R/G-PO/N14'R/G		PO/N 56' B/Y (1-way ANOVA)	
F Value for Age Groups	1.23		1.86		2.39		0.78	
DF	5,54	NS	5,54	NS	5,54	NS	4,45	NS
F Value for Stimuli	0.36		0.11		0.88		N/A	
DF	1,54	NS	1,54	NS	1,54	NS		
F Value for Interaction	1.39		0.61		0.54		N/A	
DF	5,54	NS	5,54	NS	5,54	NS		

Table 5.22 Showing the levels of significance on comparing the CI CII configuration for two types of stimulation for progressive age group analysis. (Results are shown for right eye only).

The responses to coloured stimulation are also delayed (Figure 5.9). The pattern reversal and flash responses of these subjects are within normal limits.

These results support 1) the statement made by van der Tweel et al. (1979) that the responses appear always to contain CII with the other components being inconsistent and 2) the findings of Lesevre and Joseph (1980) who obtained large variabilities in normals for the onset-offset components. This greater variability of the responses to pattern onset-offset stimulation could be explained by Drasdo's (1982) observations, that whereas the pattern onset response is subject to many local variations, the pattern reversal is less so and the flash response is very similar on all electrodes in the occipital surrounding areas. It may be that for pattern onset-offset stimulation to be successfully used, surface mapping has to be performed as suggested by Jeffreys (1980) and Darcey et al. (1981) however, this would be time-consuming for clinical purposes.

The other components of the onset-offset response appeared in both eyes in the following percentage for 56' black/white stimulation; CI - 91.7%; CIII - 78.3% and the off-response - 65% . It has been observed that if a subject's responses lack any of these components to one form of stimulation, this is not necessarily the case for another form of stimulation, the percentage appearance for red/green 56' and blue/yellow 56' stimulation respectively are as follows: CI - 81.7%, 78.8%; CIII - 45%, 33.3% and the off-response - 63%, 45.5%.

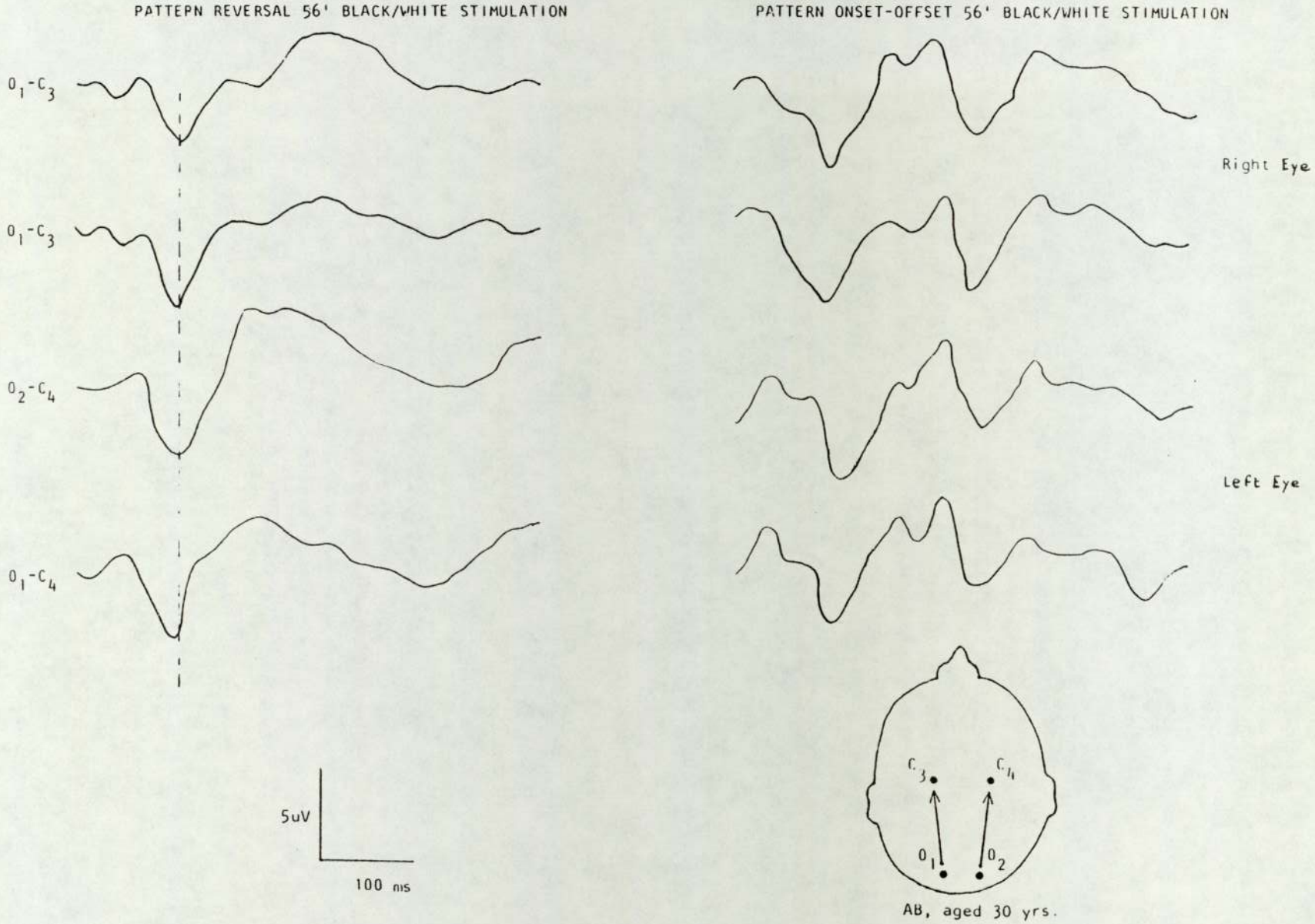


Figure 5.9 The VERs of a visually clinically normal subject whose pattern reversal responses are within normal limits, however, the pattern onset-offset responses are poorly formed and shifted in latency

In the repeatability study which was performed on 10 subjects, the only component which is seen in all of the initial and repeated traces, is CII. For 56' black/white stimulation, CI is seen in 7 of the 9 subjects (77.8%) on both occasions with CIII and the off-response being less consistent in appearance, 66.7% and 55.6% respectively (see appendix 7).

5.1.2 Psychophysical Results

Visual Fields

Although the data for the visual fields has been analysed by the Wilcoxon test for discrete values (Witte, 1980) it is thought that the age changes would be best illustrated by the mean values of the macular thresholds for white and coloured lights which are shown in Figure 5.10. The range of macular threshold values is given in Table 5.23. Similar to the electrophysiological data, there is a relatively sharp decline in sensitivity in the 50+ age group. The logarithmic values for blue are quite low for normals of the older age groups, therefore making it difficult to assess abnormal pathological values.

On calculating the percentage change in the filter densities of the macular thresholds between the youngest and oldest age groups, it can be seen that the greatest change took place for blue light, followed by red, green and finally , white light. (Table 5.24). This result would indicate the greater deterioration of the colour mechanisms in comparison to the white mechanism (luminance). Although

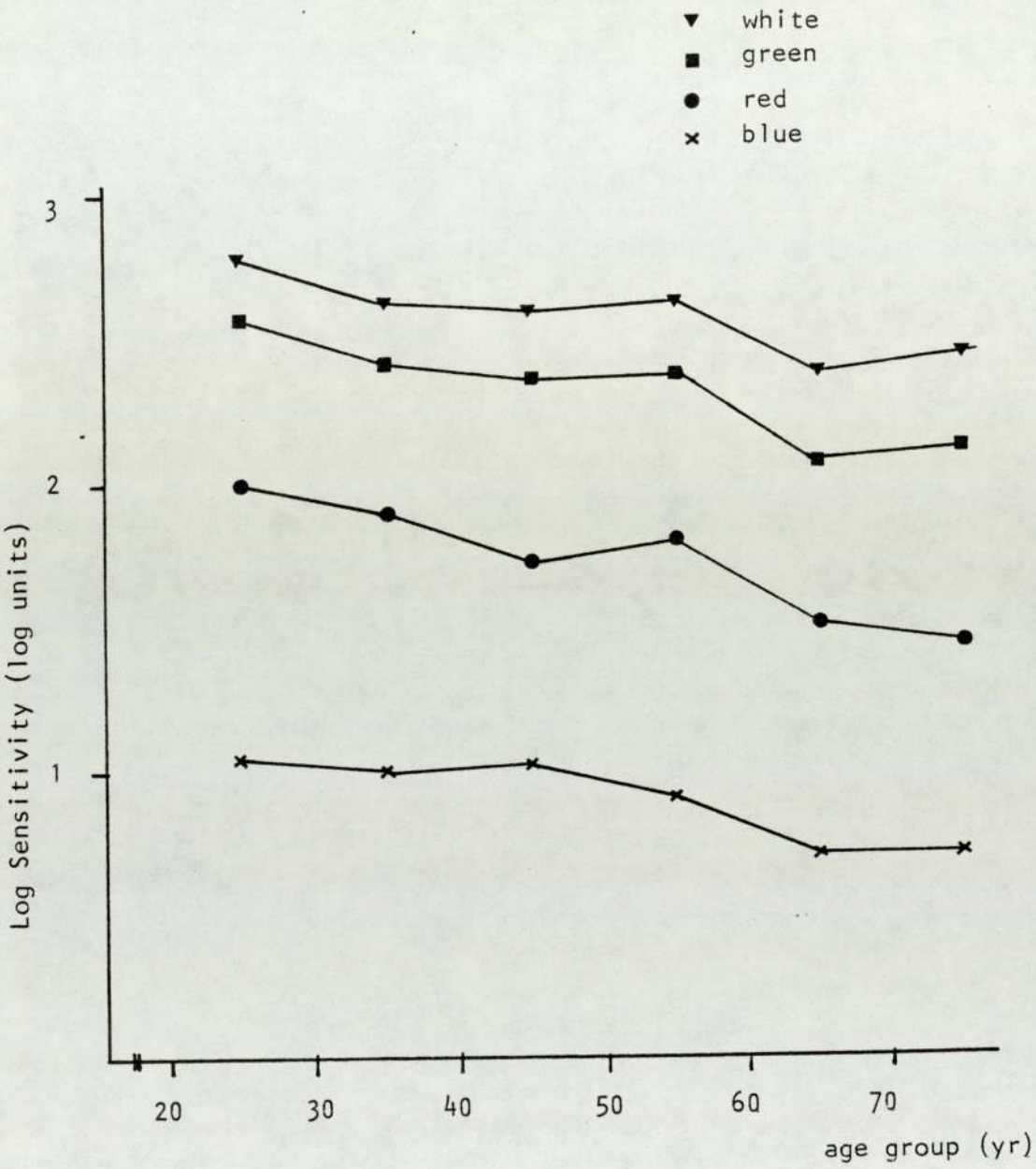


Figure 5.10

Graph showing mean log sensitivity of the macular thresholds to white and coloured light for each age group of normal subjects.

(Results are shown for right eye only).

Age Range	White	Red	Green	Blue	Visual Field Score
20-29	2.76±0.09/ 2.73±0.13 (2.6-2.8)(2.6-2.8)	2.00±0.15/ 1.93±0.18 (1.8-2.2)(1.8-2.2)	2.56±0.16/ 2.55±0.16 (2.4-2.8)(2.4-2.8)	1.04±0.17/ 1.05±0.18 (0.8-1.2)(0.8-1.2)	238.44±9.28 / 239.13±10.62 (2.0-2.6) (2.2-2.6)
30-39	2.64±0.14/ 2.68±0.14 (2.4-2.8)(2.4-2.8)	1.92±0.30/ 1.92±0.27 (1.6-2.2)(1.6-2.2)	2.42±0.19/ 2.48±0.0.21 (2.2-2.6)(2.2-2.6)	1.00±0.18/ 1.04±0.19 (0.8-1.2)(0.8-1.2)	237.30±9.41 / 238.19±10.66 (2.2-2.6) (2.2.2.6)
40-49	2.60±0.17/ 2.66±0.17 (2.2-2.8)(2.2-2.8)	1.74±0.27 1.70±0.21 (1.4-2.2)(1.4-2.2)	2.36±0.14/ 2.37±0.16 (2.2-2.6)(2.2-2.6)	1.02±0.12/ 1.02±0.12 (0.8-1.2)(0.8-1.2)	225.2±12.0 / 225.3±12.70 (1.8-2.6) (1.8-2.6)
50-59	2.64±0.15/ 2.62±0.17 (2.4-2.8)(2.4-2.8)	1.70±0.10/ 1.75±0.14 (1.6-2.0)(1.6-2.0)	2.36±0.19/ 2.40±0.19 (2.2-2.6)(2.2-2.6)	0.90±0.11/ 0.90±0.11 (0.8-1.0)(0.8-1.0)	211.46±10.49/ 210.97±10.61 (1.6-2.4) (1.6-2.4)
60-69	2.36±0.22/ 2.40±0.22 (2.0-2.6)(2.0-2.6)	1.50±0.16/ 1.52±0.18 (1.2-1.8)(1.2-1.8)	2.06±0.25/ 2.16±0.33 (1.8-2.4)(1.8-2.4)	0.72±0.15/ 0.77±0.15 (0.4-1.0)(0.4-1.0)	190.53±8.32 / 189.37±6.82 (1.4-2.4) (1.4-2.4)
70 & over	2.44±0.21/ 2.42±0.21 (2.0-2.6)(2.0-2.6)	1.44±0.23/ 1.44±0.28 (1.2-1.8)(1.2-1.8)	2.12±0.19/ 2.09±0.25 (1.8-2.4)(1.8-2.4)	0.72±0.20/ 0.78±0.22 (0.4-0.8)(0.4-0.8)	169.16±10.77/ 170.58±8.88 (1.4-2.2) (1.4-2.0)

Table 5.23 Giving the (means ± 1SD) and ranges for the macular thresholds and visual field scores for each age group of normal subjects.

Type of Stimulus	Mean Filter Density (log units)		Difference Between Filter Densities.	% Change in Filter Densities
	20-29 age gp	70-79 age gp		
White	2.76	2.44	0.32	$\frac{0.32}{2.76} \times 100 = 11.6$
Red	2.00	1.44	0.56	$\frac{0.56}{2.00} \times 100 = 28.0$
Green	2.56	2.12	0.44	$\frac{0.44}{2.56} \times 100 = 17.2$
Blue	1.04	0.72	0.32	$\frac{0.32}{1.04} \times 100 = 30.8$

Table 5.24 Showing the percentage change in the mean log sensitivity of the macular thresholds for the youngest and oldest age groups in normal subjects. (Results shown for right eye only).

the fovea is not the optimum retinal location at which to assess the blue threshold, this does not negate the above observation.

The mean values for white visual field testing are shown in Table 5.23. However, the initial filter densities used for testing each age group have been chosen according to the results obtained in a pilot study (see appendix 3).

The Fusion Thresholds to Flicker Stimulation at 3, 10 and 30 Hz

The mean log sensitivities for flicker stimulation are presented for each age group in Table 5.25 and illustrated in Figure 5.11. It is seen that at each frequency, there is a decrease in the flicker sensitivity with increasing age. The decrease in log flicker sensitivity for 30 Hz is so much more rapid than for the two lower frequencies, that the interaction variance ratio attained significance ($p<0.01$; Table 5.26, Figure 5.11). These results would indicate that both the activity of the tonic and phasic cells deteriorate with age, as the area stimulated by flicker in this study is the central 2^{o} in which there should be a large presence of tonic cells with the phasic cells being more common in the parafoveal retina than in the foveal retina (Gouras and Zrenner, 1979). There is also the influence of the flickering stimulus being yellow, whereby the increased lens absorption of short and middle wavelengths, as well as the retinal changes which occur might be two reasons for the high flicker thresholds and greater variability in the results with increasing age, especially at the high frequencies.

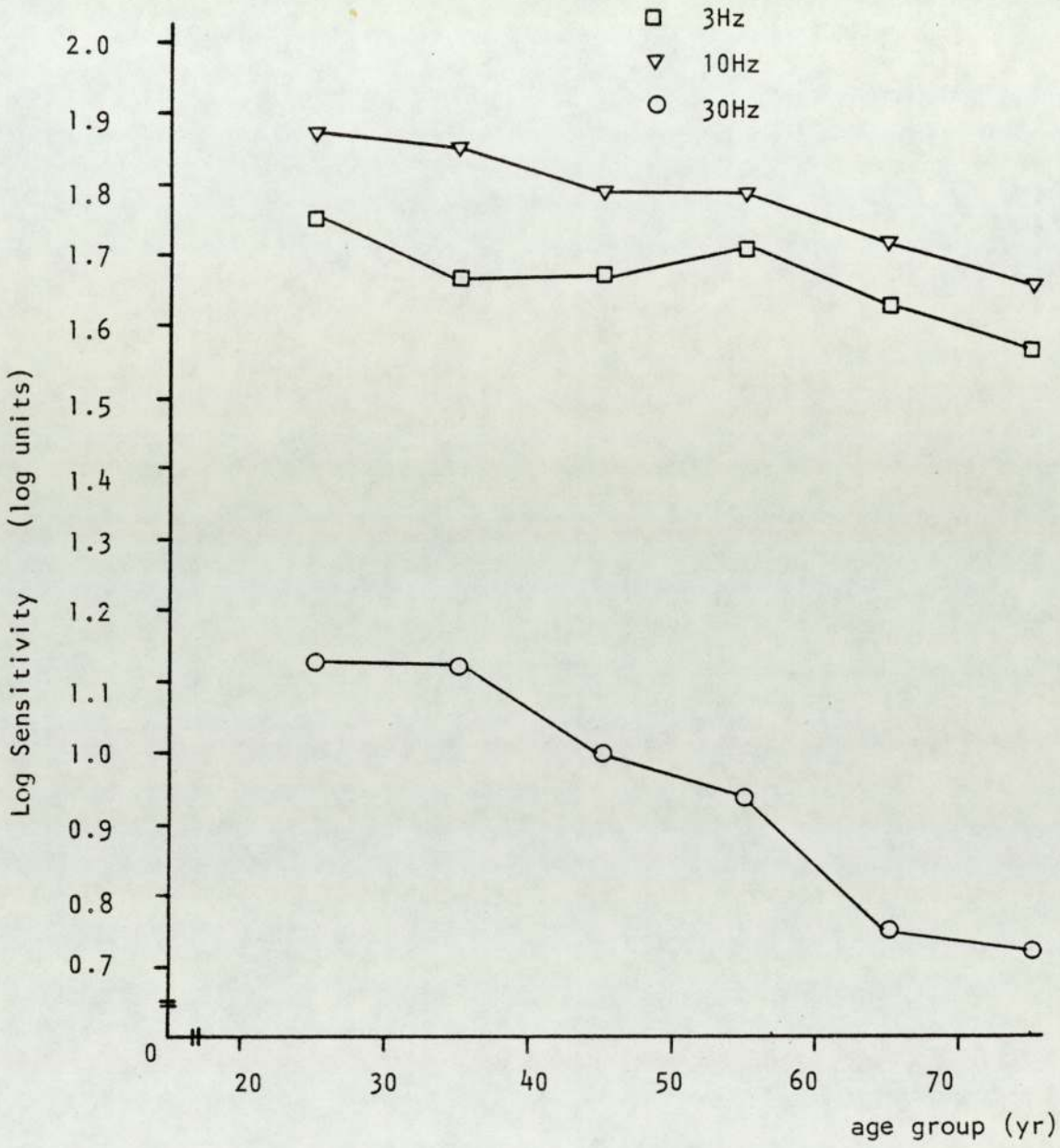


Figure 5.11

Graph showing mean log sensitivity of the flicker fusion thresholds at three representative flicker frequencies for each age group of normal subjects.

(Results are shown for right eye only).

Average	LOG SENSITIVITY (log units)		
	3 Hz	10 Hz	30 Hz
20-29	1.7532 ± 0.1131 / 1.7596 ± 0.1160	1.8693 ± 0.0582 / 1.8310 ± 0.0976	1.1255 ± 0.1298 / 1.1707 ± 0.1647
30-39	1.6710 ± 0.0575 / 1.6860 ± 0.0296	1.8512 ± 0.0965 / 1.8542 ± 0.0501	1.1108 ± 0.1187 / 1.1086 ± 0.1001
40-49	1.6799 ± 0.0859 / 1.6602 ± 0.0735	1.7938 ± 0.1007 / 1.7870 ± 0.1218	1.0035 ± 0.1801 / 0.9797 ± 0.1582
50-59	1.7071 ± 0.069 / 1.7071 ± 0.0712	1.7889 ± 0.0805 / 1.7873 ± 0.0877	0.9428 ± 0.2201 / 0.9443 ± 0.2261
60-69	1.6263 ± 0.0806 / 1.6551 ± 0.0658	1.7202 ± 0.1008 / 1.7486 ± 0.0926	0.7496 ± 0.1449 / 0.7718 ± 0.1576
70 & Over	1.569 ± 0.1148 / 1.5784 ± 0.1322	1.6567 ± 0.1184 / 1.6685 ± 0.1148	0.7164 ± 0.0974 / 0.7174 ± 0.0853

Table 5.25 Giving the means ± 1SD of the sensitivities of the flicker fusion thresholds at three representative frequencies for each age group of normal subjects

F Value	Type of Stimulus 3Hz - 10Hz - 30Hz
F Value for Age Groups DF	15.10 5,54 p<0.01
F Value for Stimuli DF	1292.22 2,108 p<0.01
F Value for Interaction DF	4.68 10,108 p<0.01

Table 5.26

Showing the levels of significance for the log sensitivity of the flicker fusion thresholds for progressive age group analysis at 3 flicker frequencies. (Results are shown for right eye only).

It has been reported that the higher frequencies are more severely affected than the lower frequencies by a reduction in luminance level (Kelly, 1961, 1964) which could be caused by the decrease in pupil size with progressive age. In this study, it has already been mentioned that the decrease in pupil size with age leads to a 0.35 log unit reduction in retinal illuminance. It has been found by a small experimental study performed on two subjects ($\bar{x} = 25.5 \pm 3.5$ yr), that a 0.4 log unit* reduction in retinal illuminance, produced a reduction in flicker sensitivity of approximately 0.6607 log units at 30 Hz. This was repeated for reductions in retinal illuminance of 0.3, 0.2 and 0.1 log units, when values of 0.5030, 0.3652 and 0.1329 log units respectively were obtained for the reduction in flicker sensitivity at 30 Hz. On inspecting Table 5.25). it can be seen that at 30 Hz the reduction in flicker sensitivity between the 20+ and 70+ age groups is equal to 0.4091 log units (1.1255 - 0.7164), which is less than the value indicated experimentally. If, however, the reduction in flicker sensitivity is taken between the 40+ and 70+ age groups (whereby the reduction in pupil diameter is equivalent to a 0.121 log unit reduction in retinal illuminance), then the reduction flicker sensitivity is 0.2821 log units (1.0035 - 0.7164). On examining the experimental results above for a 0.1 log unit reduction in retinal illuminance, it is seen that the value of 0.1329 is substantially less than the actual value for the reduction in flicker sensitivity. Hence, these results

* Please note that "retinal illuminance" and "flicker sensitivity" are expressed in log units but they are not to be confused.

would suggest that although the reduction in pupil size with age is a contributing factor to the rapid decline in the slope of log flicker sensitivity versus age at 30Hz, (Figure 5.11), it certainly does not appear to be the only contributing factor. It is also indicated that the age effect occurs mostly from the fourth decade onwards at this frequency which can be seen in Figure 5.11.

From the data of both the electrophysiological and psychophysical tests, it is indicated that the reduction in sensitivity to luminance - and spatially-modulated stimuli for white and coloured stimulation does not become manifest in an obvious manner until the fifth decade, with a fairly rapid deterioration thereafter.

For all of the tests used, no significant interocular differences have been obtained.

5.2 Data for Chronic Alcoholic Subjects

For the initial investigation, the results of 21 alcoholic subjects have been compared to those of 21 age-and-sex matched control subjects. For the repeat investigation, the data of 10 alcoholics (as the other failed to return) have been compared for the two investigations. (Table 5.27).

5.2.1 Electrophysiological Results

From Table 5.28, it is seen that the component of the dark-adapted ERG which is significantly different between alcoholics and controls is the peak latency of the B wave ($p < 0.01$). Although the amplitude of the AB configuration is considerably lower in the alcoholics than in the controls, the difference has not reached significance (Table 5.28).

For the photopic ERG, the peak latency of the B wave also reaches a significant level ($p < 0.05$). The mean amplitude of the AB configuration for the alcoholics is increased in comparison to the controls because 2 alcoholic subjects (7, 19; 173 uV and 208 uV respectively for right eye) demonstrated supranormal amplitudes. Nevertheless, there is no significant difference between the mean amplitudes of the two groups. The peak latencies of the A wave and OPs are not markedly different although the second OP is poorly formed in 3 alcoholic cases (14, 15, 20), (Figure 5.12).

The increase in the peak latency of the B wave is supported by Levett and Morini's (1978) findings on the light-adapted ERG, that the

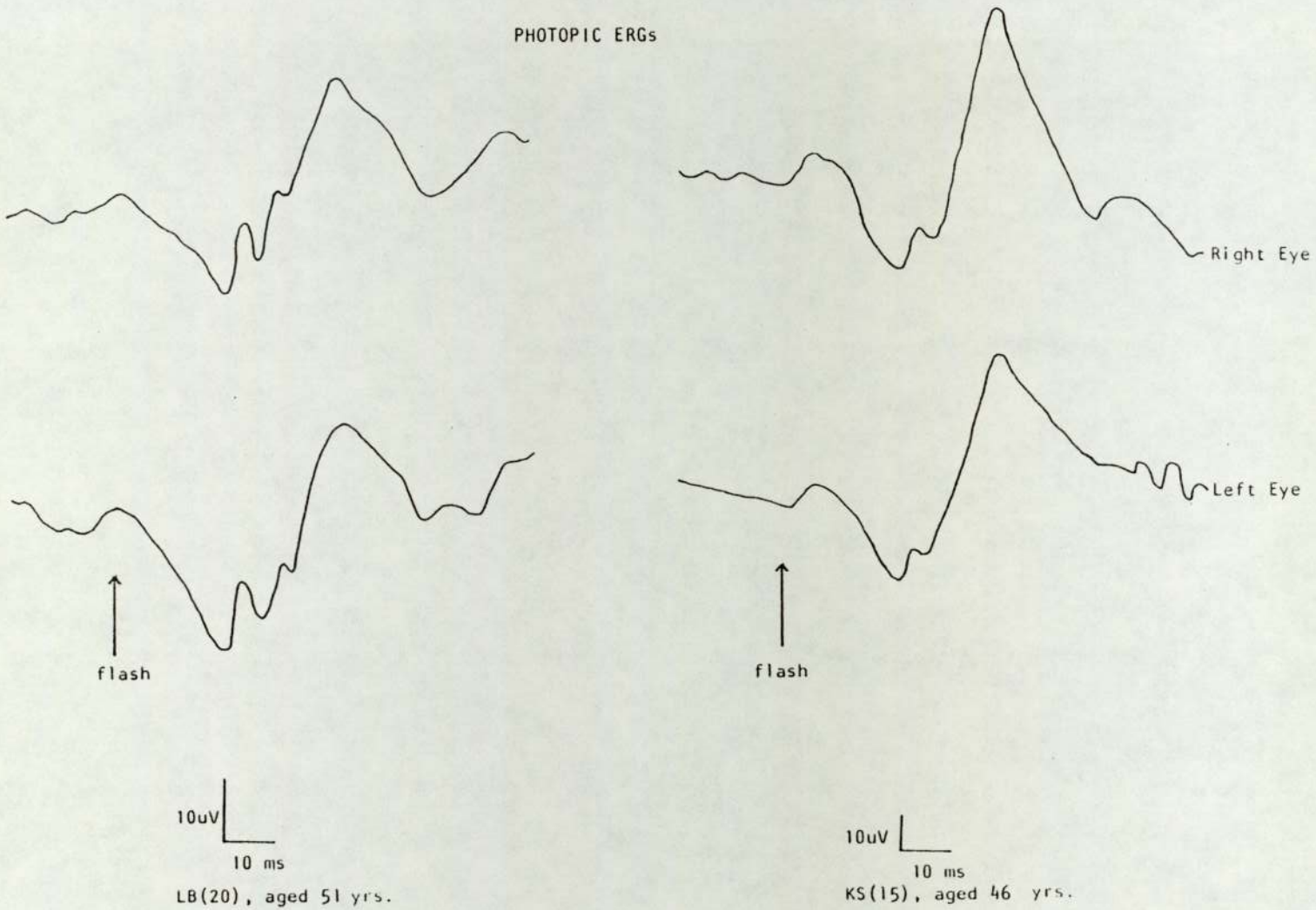


Figure 5.12 The photopic ERGs of two chronic alcoholic subjects whose responses demonstrated a reduction and abolition in the second OP respectively, accompanied by a reduction in the first OP in subject KS (15)

Subject Age Sex	Visual Acuity RE/LE 1st Visit RE/LE 2nd Visit	Pupil Size (mm)	Ocular Changes	Smoking Habits/Period of Smoking(yr)	Alcohol Intake Per Day	Period of drinking/ Period of Heavy Drinking (Yr).	Body Weight (Kg)/ Appetite.	Period of Abstinence Before 1st Visit (days)	Period Between Visits.	Medication 1st Visit	Medication 2nd Visit	Other Illnesses Including Neurological Changes
GJ 24 M 1	6/5 N5 . 6/5 N5	5/5 A	NAD	Non-smoker	0.7-1.4 l wine 1.1-3.4 l beer	10/3	73.5 Good	12/52	FTR	None	FTR	Pancreatitis 4 years ago.
DS 26 M 2	6/5-1 N5 6/5 N5	4.5/4.5A	NAD	Non-smoker	0.35 l whiskey 2.3l l beer	12/4	65 Good	5/52	FTR	None	FTR	DT's
LT 28 M 3	6/5 N5 6/5 N5	6/6A	NAD	60 cig/day 15	6.8 l beer	13/1	76 Poor	1	FTR	None	FTR	-
JB 31 F 4	6/5-3 N5 6/5-2 N5	6/6A	NAD	30-40 cig/day 10	Up to 12 l cider	7/7	57 Fair	4	FTR	1 inj. Parentrovite	FTR	DT's Depression.
PS 33 M 5	6/5 N5 6/5 N5	6/6A	NAD	Non-smoker	Variable Intake Barley wine, dry wine, bitter, home brewer, methylated spirits.	17/13	65 Poor	5	FTR	Sodium Valproate	FTR	Epileptic for 13 years, only when drinking.
GR 34 M 6	6/9+3 N6 6/9+1 N6 6/9+3 N6 6/9+3 N6	6.5/6.5S 6/6S	NAD	25-30 cig/day 20	8.5 - 9 l bitter 3 l whiskey	12/7	62 Poor	4	11/52	1 inj. Parentrovite and 6 tablets Valium	None-Stopped Valium 5 wk before 2nd visit.	-
DD 36 M 7	6/5-1 N5 6/5 N5 6/5 N5 6/5 N5	4.5/4.5S 5/5A	NAD	30 cig/day 16	5.7 l beer 2.1 l sherry Surgical Spirits	20/15	77 Poor	6/52	6/52	None	None	-
JT 37 M 8	6/5-3 N5 6/5-2 N5	6/6A	NAD	15-20 cig/day 17	0.5 l vodka 2.3 l bitter	17/12	69 Good	3	FTR	None	FTR	DT's Depression
JE 37 M 9	6/6 N5 6/6 N5	5/5A	NAD	25 cig/day 17	0.35 l brandy Variable intake of cider and beer.	21/19½	78.6 Good	3/52	FTR	Motival for 5 days	FTR	DT's Anxiety.
POC 38 M 10	6/5-3 N5 6/5 N5	6/6A	NAD	15g rolling tobacco/day 24	11 l cider plus cheap wine	25/19	70.5 Fair	5	FTR	Phenobar-bitone, Epanutin, Ospolot.	FTR	Epilepsy.
BW 38 M 11	6/6+4 N5 6/6 N5 6/6+3 N5 6/6 N5	4.5/3A 4.5/3A	UES	15g pipe tobacco/day 20	8 l cider	24/8	54 Good	8	5/52	None	None	Had an accident when 7 years old.
FO 40 M 12	6/5-2 N5 6/5 N5 6/5 N5 6/5 N5	4.5/4.5A 4.5/4.5A	NAD	Non-smoker	2-3 l sherry	19/10	63.5 Fair	2	8/52	Heminevrin for 1 day.	None	-
JH 42 F 13	6/9+1 N5 6/6 N5 6/9+3 N5 6/6 N5	5.5/5.5A 5/5A	RE$^{\Delta}$ (10$^{\Delta}$)	40 cig/day 25	4 l strong lager	4/18½	81 Fair	5	10/52	Ativan Amytrypty-line.	Ativan Amytrypty-line.	Depression with Anxiety.
JB 44 M 14	6/9+4 N6 6/9+3 N6	5/5S	NAD	20-25 cig/day 30	1 l sherry 8 l beer plus anything.	30 gradual esca-lation.	70.3 Fair	5	FTR	Heminevrin for 4 days	FTR	-
KS 46 F 15	6/6+3 N5 6/6+3 N5 6/6+3 N5 6/6+4 N5	3/3A 3/3A	NAD	50 cig/day 25	Up to 4.9 l sherry	4/9½	86.5 Poor	1	6/52	Pyrido-stigmine	Pyrido-stigmine	Myaesthenia Gravis
GL 48 M 16	6/5-1 N5 6/5-1 N5 6/5-1 N5 6/5 N5	4/4A	NAD	15g rolling tobacco/day 32	0.7 l spirits 4.5 - 5.7 l lager.	35/28	85 Poor	2	8/52	1 inj. Parentrovite	None	Considerable liver damage, DT's.
JT 48 M 17	6/5-3 N5 6/5-3 N5	2.5/2.5A	NAD	20 cig/day 28	0.35 l whiskey 2 l cider 1.7-2.3 l bitter	31/3½	69.5 Good	5	FTR	None	None	Trauma to head 6 weeks ago.
TG 49 M 18	6/5-1 N5 6/5-1 N5 6/5-2 N5 6/5-2 N5	5/5A	NAD	Non-smoker	6.8 l lager	30/5	69 Good	5	5/52	Librium for 5 days	Librium	DTs.
JG 50 F 19	6/6+3 N5 6/6+1 N5 6/5-4 N5 6/5-2 N5	5.5/5.5A	NAD	20 cig/day 25	1 l sherry	11/10 Drinks in bouts	54 Fair	4/52	6/52	None	None	Depression
LB 51 M 20	6/6 N6 6/6 N5	4.5/4.5S	NAD	15 cig/day 36	Up to 0.7 l whiskey.	34/ gradual esca-lation.	68.9 Poor	5	FTR	None	FTR	2 operations for peptic ulcers, liver enlarged, suspected liver disease.
MM 52 M 21	6/6-1 N5 6/18+1N14 6/6-2 N5 6/12 N10	4/4A 4.5/4.5A	NAD	Non-smoker	8.5 l lager	26/ gradual esca-lation.	76 Poor	3	7/52	Heminevrin for 2 days Glibencl-amide, Glu-cophage.	Glibencl-amide, Glucophage.	Diabetic, liver enlarged.

Key: A = Active; I = Inactive; S = Sluggish; RE = Right Eye; LE = Left Eye; cig = Cigarette; FTR = Failed to Return.
DT's = Delirium Tremens; UES = Unequal Pupil Size; RE$^{\Delta}$ = Right Exotropia.

Table 5.27 giving the particulars of the 21 chronic alcoholic subjects

	Dark-Adapted Low Intensity					Photopic				
Subject Group	A(ms) R	A(ms) L	B(ms) R	B(ms) L	AB (uV) R	AB (uV) L	A(ms) R	A(ms) L	B(ms) R	B(ms) L
1	25.94±2.32/ 26.59±1.76		49.61±2.67/ 50.15±1.98		231.06±67.82/ 225.53±63.39		19.90±1.22/ 19.60±1.29		42.40±1.99/ 42.74±2.45	
2	25.27±1.92/ 25.04±1.89		48.08±2.70/ 48.16±2.64		256.38±38.87/ 254.01±36.92		20.04±1.23 20.10±1.46		41.02±2.45/ 41.21±2.54	
F Value for Eyes DF	0.74 1,20	NS	1.54 1,20	NS	0.61 1,20	NS	1.97 1,20	NS	2.28 1,20	NS
F Value for Groups DF	4.19 1,20	NS	9.65 1,20	$p<0.01$	2.70 1,20	NS	0.81 1,20	NS	4.39 1,20	$p<0.05$
F Value for Interaction DF	4.55 1,20	$p<0.05$	0.69 1,20	NS	0.27 1,20	NS	1.38 1,20	NS	0.15 1,20	NS

	Photopic					
Subject Group	OP_1 (ms) R	OP_1 (ms) L	OP_2 (ms) R	OP_2 (ms) L	AB(uV) R	AB(uV) L
1	25.06±1.45/ 25.26±1.59		32.06±1.33/ 32.10±1.38		95.96±53.80/ 96.33±55.81	
2	24.95±1.58/ 24.94±1.83		31.57±1.80/ 31.69±1.84		88.15±23.17/ 88.21±21.22	
F Value for Eyes DF	0.34 1,20	NS	0.39 1,20	NS	6.14×10^{-3} 1,20	NS
F Value for Groups DF	0.21 1,20	NS	0.79 1,20	NS	0.34 1,20	NS
F Value for Interaction DF	0.40 1,20	NS	0.13 1,20	NS	3.19×10^{-3} 1,20	NS

Key: 1: Alcoholic Subjects 2:Control Subjects.

TABLE 5.28 Giving means ± 1SD for the components of the dark-adapted and photopic ERGs for 21 alcoholic and 21 control subjects.

response (including the B wave) becomes more retarded after chronic alcohol ingestion. Although these workers reported a generally reduced ERG amplitude during alcoholic ingestion, they found that there was a transient amplitude overshoot after withdrawal from alcohol before the response settled back to a new steady state. Perhaps, this would explain the supranormal amplitudes seen in the two above-mentioned subjects (7, 19) for the photopic ERG who had abstained from alcohol for six and four weeks respectively before they were examined. In comparison to the other alcoholics, these periods of abstinence are generally longer than those for the others, and it would appear that the effects of withdrawal are still occurring at this time. Like Levett and Morini, Cinotti et al. (1970) reported a reduction in B wave amplitude for chronic alcoholism. However, the latter workers found that it was only significantly different from that of the controls for the dark-adapted ERG and not for the light-adapted ERG. In this study, there is a reduction in the mean amplitude of the dark-adapted ERG although it has not reached a significant level (Table 5.28).

The disappearance or abnormal formation of the OPs has been confirmed by other investigators in both chronic alcoholism and tobacco-alcohol amblyopia (Cinotti et al 1970; Stangos et al 1970;1977; Van Lith and Vijkvinkel-Bruinenga, 1978; Van Lith and Henkes, 1979; Levett and Morini, 1980). The OP appears to be a better indicator than the B wave, of changes occurring in the retina in these alcoholics, as its appearance is abnormal whereas the latency of the B wave is delayed but still falls within normal limits.

The OPs have been shown to be very susceptible to interference of the retinal circulation and synaptic transmission within the retina (Yonemura, 1962; Yonemura et al. 1962; Algvere, 1968; Brown, 1968; Stangos et al. 1976; Ikeda, 1976; Yonemura and Kawasaki, 1979), however their sites of origin remain controversial although many investigations indicate the inner part of the retina as the likely source (Yonemura et al, 1963; Brown, 1968; Algvere, 1968; Ogden, 1973). Brown (1968) suggested that the OPs depend upon neural feedback circuits with various retinal locations in different species.

The general increase in peak latency of the B wave for both the dark adapted and photopic ERGs, indicate an alteration in rod and cone activity accompanied by a slowing of nerve impulses. As both the B wave and the OPs have been affected, it would appear that the inner rather than the outer retinal layers have been more affected, possibly with bipolar and amacrine cell involvement and even the dendrites of the ganglion cells. The reduction in mean amplitude of the AB configuration for the dark-adapted ERG is not significantly different from that of the controls although Cinotti et al. (1970) reported markedly depressed values for chronic alcoholics for the dark-adapted but not for the light-adapted ERG. The difference in significance between the two studies does not seem to be due to the increased pupil size in alcoholics as artificial pupils were not used in either study. However, it could be due to the difference in the condition of the alcoholics in Cinotti et al's study and those in this study. The alcoholics in the former study all suffered from chronic liver disease whilst only four alcoholics in this

study have abnormalities of the liver. It has been reported that alcoholic cirrhotics are often zinc deficient leading to abnormal dark-adaptation abilities (Morrison et al. 1978). It is believed that zinc may enhance the mobilisation of vitamin A from the liver and/or the activity of alcoholdehydrogenase (an enzyme which transforms retinal to retinaldehyde which is in turn necessary for rhodopsin formation) in the retinal activities (Yolton, 1981).

On repeating 10 alcoholic subjects after approximately eight weeks, no marked changes are seen for the peak latencies or amplitudes of the components of the dark-adapted or photopic ERGs (Table 5.29) The latency of the dark-adapted B wave which is less delayed on the second investigation just failed to reach significance. However, the second OP reappeared in one subject (15) who is the only one to be retested out of the patients with depressed OPs.

Visual Evoked Responses

The results for the VERs to flash stimulation demonstrate a significant difference ($p<0.05$) between the mean P_2 latency for the chronic alcoholics and controls (Table 5.30). The results of one subject (21) whose flash responses were very poorly formed on the first investigation and therefore had to be omitted from the statistical analysis, showed an identifiable waveform on the second investigation (Figure 5.13a). It is interesting to note that this subject had diabetes but he was not taking his medication for some time previous to hospital admission. Nevertheless, this subject revealed dis-

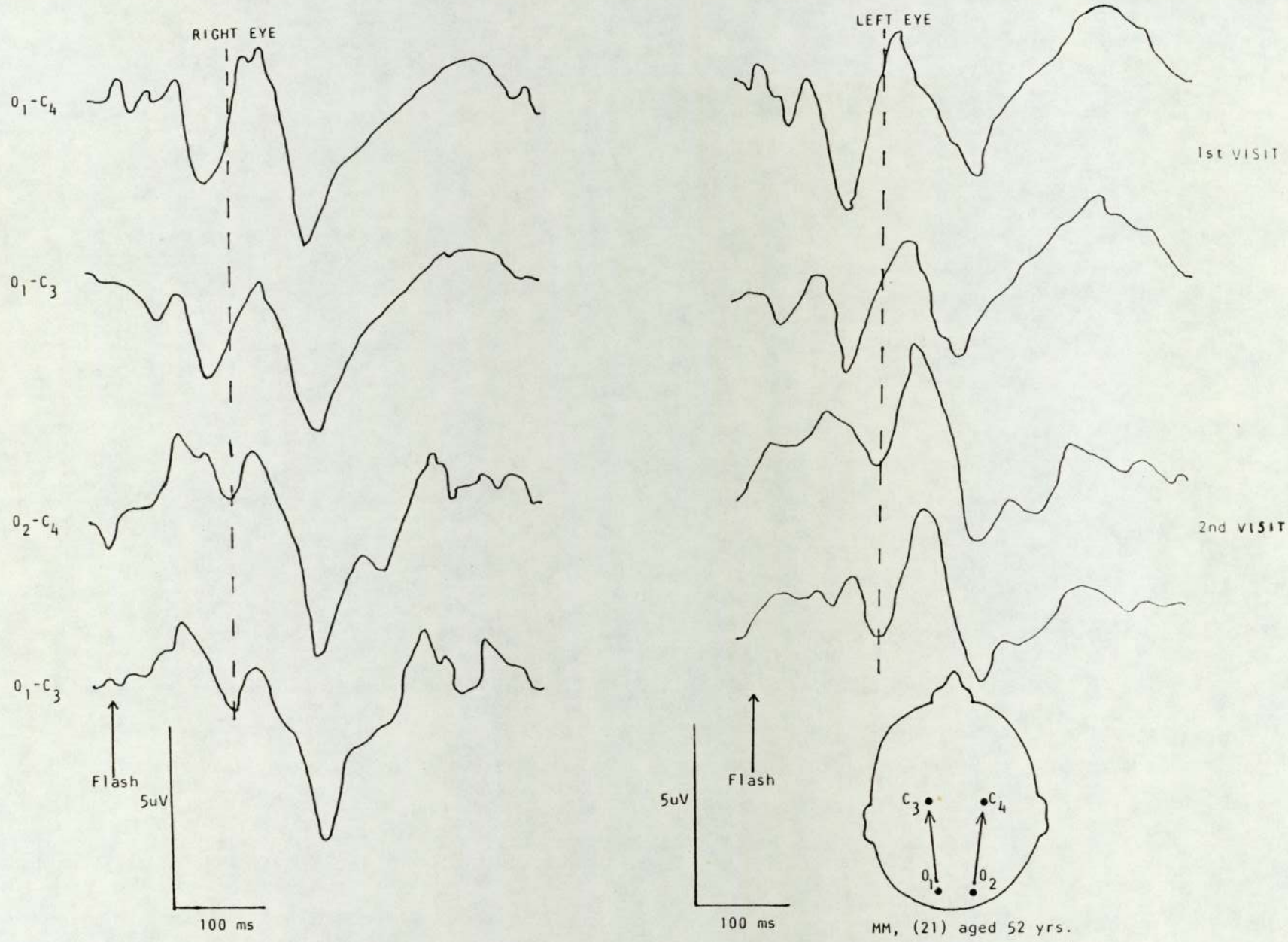


Figure 5.13a The flash VERs of a chronic alcoholic who did not demonstrate a P2 component on the first investigation but it appeared on the second investigation (although it was still of low amplitude) after cessation of alcohol

	Dark-Adapted Low-Intensity					Photopic			
No. of Visit.	A (ms) R L	B (ms) R L	AB(uV) R L	A (ms) R L	B (ms) R L	OP_1 (ms) R L	OP_2 (ms) R L	AB (uV) R L	
Visit 1	26.99±1.84/ 27.27±1.70	50.38±2.76/ 50.60±2.08	203.61±59.33/ 207.58±56.70	19.78±1.43 19.15±1.51	41.53±1.61/ 41.53±1.70	25.08±1.69/ 25.20±1.79	32.03±1.64/ 32.28±1.82	101.64±52.13/ 106.36±53.45	
Visit 2	27.10±1.16/ 27.25±1.45	49.68±2.13/ 49.88±2.04	231.00±62.66/ 234.23±65.88	20.30±0.98/ 20.00±0.78	42.03±2.05/ 41.83±1.99	25.05±1.06/ 25.38±1.40	32.15±1.38/ 32.00±1.41	100.16±18.63/ 103.91±23.79	
F Value for eyes DF	0.87 1,9	NS	0.34 1,9	NS	0.34 1,9	NS	5.75 1,9	$p<0.05$	0.23 1,9 NS	0.90 1,9 NS	0.07 1,9 NS	1.18 1,9 NS
F value for visits DF	0.02 1,9	NS	4.54 1,9	NS	2.42 1,9	NS	3.56 1,9	NS	0.65 1,9 NS	0.04 1,9 NS	0.04 1,9 NS	0.02 1,9 NS
F value for interaction DF	0.12 1,9	NS	2.56×10^{-3} 1,9	NS	6.08×10^{-3} 1,9	NS	0.80 1,9	NS	0.50 1,9 NS	0.30 1,9 NS	1.62 1,9 NS	0.02 1,9 NS

TABLE 5.29 Giving means ± 1SD for the components of the dark-adapted and photopic ERGs for 10 alcoholic subjects who have been repeated.

Subject Group	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L
1	130.26±6.33	131.42±47.48	5.13±3.08	5.63±3.34
2	125.30±8.97	125.97±9.22	6.27±3.67	6.57±3.09
F Value for Eyes DF	0.79 1,18	NS	1.48 1,18	NS
F Value For Groups DF	4.44 1,18	$p < 0.05$	1.10 1,18	NS
F Value for Interaction DF	0.27 1,18	NS	0.08 1,18	NS

Key: 1: Alcoholic Subjects 2: Control Subjects

TABLE 5.30 Giving means ± 1SD for the P_2 component and N_2P_2 configuration for flash stimulation in 19 alcoholic and 19 control subjects.

cernible pattern responses to the larger check size (56') on the first occasion with an improvement in the VERs to the smaller check size (14') on the second occasion.

The results of two other alcoholic subjects (2, 13) have been omitted as their VERs were greatly marred by muscular activity as these patients were extremely tense throughout the investigation.

For pattern reversal stimulation, the latencies of the P_2 component for 56' black/white and coloured stimulation do not reveal any marked difference between the alcoholics and controls. For blue/yellow stimulation the data of one subject (20) has not been included in the analysis as his responses were indiscernible (this subject is suspected of having liver disease) with no improvement on the second investigation (Table 5.31-5.33).

The P_2 latencies to the smaller check size (14') attain a higher level of significance for black/white stimulation than for red/green stimulation ($p<0.01$ and $p<0.05$ respectively). However, this does not reflect the true nature of the data, as only one subject (20) did not give discernible VERs to black/white stimulation but there were 3 additional subjects (3, 14, 21) who demonstrated poorly formed responses and had to be eliminated from the data for red/green stimulation. On omitting the data of these 4 subjects from the statistical analysis for black/white stimulation, the level of significance is lowered to 5% (F value, 6.65; DF, 1,14). From these results it would therefore appear that red/green stimulation is more sensitive than black/white stimulation to

Subject Group	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L
1	106.05±6.03	105.04±5.27	4.21±1.79	4.17±2.06	110.54±7.99	109.94±8.08	3.27±1.07	3.32±1.20
2	104.24±5.27	105.18±5.41	5.19±2.17	4.91±1.99	104.54±5.41	103.92±5.67	3.93±1.65	4.20±2.54
F Value for Eyes	7.44×10^{-3}		1.36		1.15		0.72	
DF	1,18	NS	1,18	NS	1,17	NS	1,18	NS
F Value for Groups	0.25		2.07		8.79		2.21	
DF	1,18	NS	1,18	NS	1,17	$p<0.01$	1,18	NS
F Value for Interaction	5.05		0.44		5.63×10^{-3}		0.50	
DF	1,18	$p<0.05$	1,18	NS	1,17	NS	1,18	NS

TABLE 5.31 Giving means ± 1 SD for the P_2 component and N_2P_2 configuration for pattern reversal black/white stimulation (56' and 14') in 19 alcoholic and 19 control subjects.

Subject Group	P_2(ms) R	L	N_2P_2(uV) R	L	P_2(ms) R	L	N_2P_2(uV) R	L
1	113.37±7.58/114.05±8.49		3.63±1.52/3.45±1.14		115.12±6.91/115.15±8.05		2.34±1.47/2.59±1.69	
2	109.80±5.26/110.00±4.13		4.13±1.82/4.05±1.73		108.95±5.59/108.88±5.92		3.79±1.32/3.76±1.75	
F Value for Eyes	0.31		1.10		6.37×10^{-4}		0.65	
DF	1,18	NS	1,18	NS	1,14	NS	1,18	NS
F Value for Groups	2.70		1.35		5.85		10.87	
DF	1,18	NS	1,18	NS	1,14	$p<0.05$	1,18	$p<0.01$
F Value for Interaction	0.13		0.15		0.02		1.30	
DF	1,18	NS	1,18	NS	1,14	NS	1,18	NS

TABLE 5.32. Giving means ± 1SD for the P_2 component and N_2P_2 configuration for pattern reversal red/green stimulation (56' and 14') in 19 alcoholic and 19 control subjects.

Subject Group	P_2(ms) R	L	N_2P_2(uV) R	L	CII(ms) R	L	CI CII (uV) R	L
1	114.03±12.63/112.42±11.63		3.13±0.85/2.95±0.78		149.88±15.08/148.79±13.39		5.35±2.29/4.63±1.62	
2	107.74±6.21/107.09±6.42		3.31±1.21/3.39±1.40		143.75±10.69/142.71±10.07		6.00±3.69/1.34±3.95	
F Value for eyes	4.16		1.54		2.29		0.49	
DF	1,17	NS	1,17	NS	1,17	NS	1,17	NS
F Value for Groups	3.94		0.19		2.57		1.54	
DF	1,17	NS	1,17	NS	1,17	NS	1,17	NS
F Value for Interaction	0.71		1.89		1.14×10^{-3}		4.45	
DF	1,17	NS	1,17	NS	1,17	NS	1,17	$p<0.05$

TABLE 5.33 Giving the means ± 1SD for the P_2 and CII components and N_2P_2 and CI CII configurations for pattern reversal and pattern onset-offset blue/yellow (56') stimulation respectively in 18 alcoholic and 18 control subjects.

changes within the macular region in this group of patients. Two of the subjects (6, 21) who did not show discernible VERs to 14' red/green stimulation in the first investigation have been repeated. The responses of the former subject (6) failed to show any improvement. However, the latter subject (21) demonstrated a delayed but discernible response from the right eye only, for pattern reversal stimulation. For onset-offset stimulation, the VER from this eye was also greatly improved in waveform and latency (Figure 5.13b).

The amplitudes of the N_2P_2 configuration to flash and pattern reversal 56' black/white and coloured stimulation do not reveal any marked differences between alcoholic and control subjects (Table 5.31). The amplitudes for 14' black/white stimulation are also insignificant, however, for 14' red/green stimulation a marked difference has been obtained ($p<0.01$; Table 5.32).

The peak latencies of the CII component for pattern onset-offset 56' black/white coloured stimulation fail to reach significance (Table 5.33-5.35). For 14' black/white and red/green stimulation, the levels of significance are 1% and 5% respectively, with two subjects (14, 20) being omitted from the red/green data due to poorly formed responses. On analysing the data for 14' black/white stimulation without these two subjects, the level of significance is 5% (F value 6.837; DF 1,16). For both pattern reversal and pattern onset-offset stimulation, the responses of these two subjects largely influence the results for black/white stimulation whilst

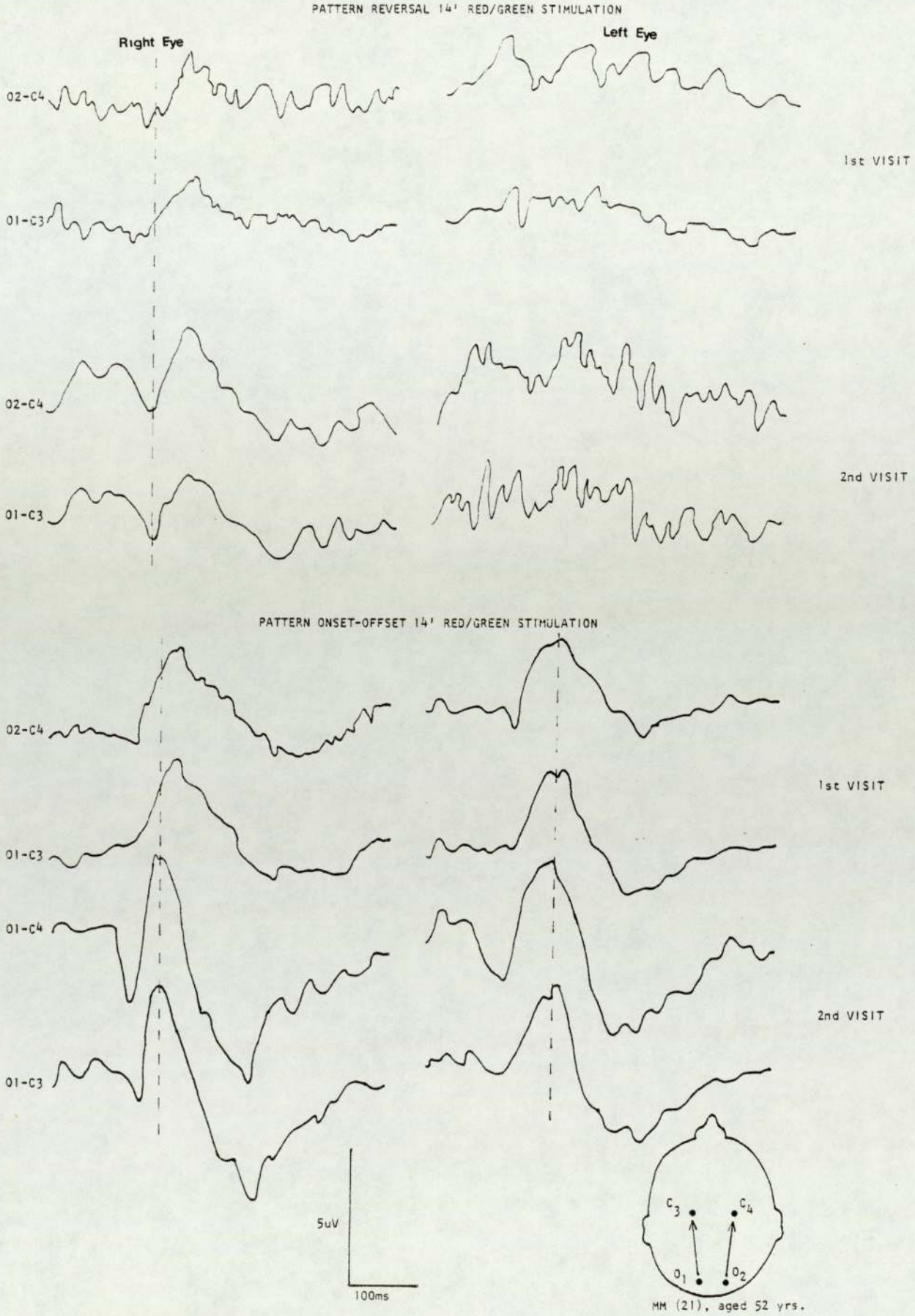


Figure 5.13b

The VERs to pattern reversal and onset-offset stimulation in a tobacco-alcohol amblyope on the first and second visits. For pattern reversal stimulation, on the second visit delayed but discernible responses are seen from the right eye only whilst for onset-offset stimulation, the VER from the right eye is also greatly improved in waveform and latency

two other subjects (6, 21) demonstrated a marked deterioration for red/green stimulation. Nevertheless, the latter two subjects elicited VERs for red/green onset-offset stimulation but not for red/green reversal stimulation. This absence of responses for reversal stimulation whilst the onset-offset responses are present has been previously reported by other workers (Reimslag et al. 1981; Howe et al. 1981).

The amplitudes of the C1 C11 configuration do not show any significant differences for any form of stimulation, even with zero values substituted for the two subjects for red/green 14' stimulation.

On comparing the results for the first and second investigations, no significant differences are observed for any form of stimulation (Tables 5.36-5.41). However, it is to be remembered that the VERs of subject 21 (who could not be included in the statistical analysis) improved on the second investigation to flash and 14' pattern stimulation. (The VERs to 56' stimulation are normal for both investigations). On the repeat investigation, a VER was elicited from the right eye to pattern reversal 14' black/white stimulation which was not seen on the previous investigation. The response from the left eye still remained indiscernible. On the other hand, VERs were elicited from each eye to 14' onset-offset stimulation but there is an interocular latency difference. The waveform of these responses is also much more clearly defined than that seen on the first investigation. The VERs to 14' red/green stimulation improved in only the right eye on the repeat investigation to both forms of pattern stimulation

Subject Group	CI(ms) R	CI(ms) L	CI CII (uV) R	CI CII (uV) L	CII (ms) R	CII (ms) L	CI CII (uV) R	CI CII (uV) L
1	108.46±12.67/108.33±13.13		4.53±2.03/4.73±2.29		130.63±14.74/130.32±15.44		2.34±1.47/2.57±1.69	
2	106.16±14.51/104.53±12.73		5.26±2.88/5.35±2.91		116.47±12.33/116.04±11.51		3.79±1.32/3.76±1.75	
F Value for Eyes DF	1.44 1,18	NS	0.70 1,18	NS	0.23 1,18	NS	0.65 1,18	NS
F Value for Groups DF	0.61 1,18	NS	0.67 1,18	NS	9.37 1,18	NS	10.87 1,18	NS
F Value for Interaction DF	0.98 1,18	NS	0.12 1,18	NS	4.91×10^{-3} 1,18	NS	1.30 1,18	NS

TABLE 5.34 Giving means ± 1SD for the CII component and CI CII configuration for black/white stimulation (56' and 14') in 19 alcoholic and 19 control subjects.

Subject Group	CII(ms) R	CII(ms) L	CI CII(uV) R	CI CII(uV) L	CII(ms) R	CII(ms) L	CI CII (uV) R	CI CII (uV) L
1	133.92±14.78	134.38±15.77	4.92±1.73	4.97±1.82	143.44±16.45	143.82±17.06	5.26±3.49	5.46±3.51
2	127.84±12.10	128.63±11.92	5.60±4.14	5.84±4.35	132.63±10.82	132.43±8.93	6.62±4.47	6.25±3.79
F Value for Eyes	0.51		1.20		0.01		0.10	
DF	1,18	NS	1,18	NS	1,16	NS	1,18	NS
F Value for Groups	2.05		0.66		6.66		11.03	
DF	1,18	NS	1,18	NS	1,16	$p<0.05$	1,18	NS
F Value for Interaction	0.04		0.49		0.20		1.74	
DF	1,18	NS	1,18	NS	1,16	NS	1,18	NS

TABLE 5.35 Giving means ± 1SD for the CII component and CI CII configuration for red/green stimulation (56' and 14') in 19 alcoholic and 19 control subjects.

No. of Visit	P_2(ms) R	L	N_2P_2(uV) R	L
Visit 1	130.11 ± 6.11 / 131.56 ± 6.76		4.42 ± 2.77 / 5.07 ± 2.41	
Visit 2	132.53 ± 5.14 / 132.58 ± 6.04		3.73 ± 1.58 / 3.66 ± 1.50	
F Value for eyes DF	0.37 1,8	NS	1.47 1,8	NS
F value for visits DF	2.33 1,8	NS	1.11 1,8	NS
F value for interaction DF	0.60 1,8	NS	1.80 1,8	NS

TABLE 5.36 Giving means ± 1SD for the P_2 component & N_2P_2 configuration for flash stimulation in 9 alcoholic subjects who have been repeated.

No. of Visit	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L
Visit 1	106.08±5.30 / 104.55±5.56		4.84±2.26 / 4.58±2.85		110.08±6.74 / 109.14±7.60		3.48±1.21 / 3.69±1.38	
Visit 2	104.30±5.42 / 104.93±5.55		4.85±1.67 / 4.91±2.01		110.61±7.37 / 107.97±8.04		3.23±1.03 / 3.42±1.07	
F value for eyes	0.37		0.24		3.34		4.92	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS
F value for visits	0.42		0.13		0.06		0.43	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS
F value for inter action	6.04		0.26		0.66		8.25×10^{-3}	
DF	1,8	$p<0.05$	1,8	NS	1,8	NS	1,8	NS

TABLE 5.37 Giving means ± 1 SD for the P_2 component and N_2P_2 configuration for pattern reversal black/white stimulation (56' and 14') in 9 alcoholic subjects who have been repeated.

No. of Visit	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L
Visit 1	113.25±9.32	113.58±9.72	3.76±1.30	3.78±1.13	113.50±9.02	116.04±9.72	2.94±0.84	2.81±1.04
Visit 2	111.00±6.36	111.83±8.11	3.84±0.74	3.65±0.79	112.54±6.76	112.64±6.42	3.07±0.70	3.33±0.44
F value for eyes	0.36		0.15		0.55		0.16	
DF	1,8	NS	1,8	NS	1,6	NS	1,6	NS
F value for visits	2.33		2.59×10^{-3}		0.52		2.41	
DF	1,8	NS	1,8	NS	1,6	NS	1,6	NS
F value for interaction	0.09		0.30		3.47		1.69	
DF	1,8	NS	1,8	NS	1,6	NS	1,6	NS

TABLE 5.38 Giving means + 1 SD for the P_2 component and N_2P_2 configuration for pattern reversal red/green stimulation ($\overline{56}$' and 14') in 9 alcoholic subjects who have been repeated.

No. of Visit	P2(ms) R	P2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L	CII(ms) R	CII(ms) L	CI CII (uV) R	CI CII (uV) L
Visit 1	117.20±10.59 / 115.15±12.33		3.25±1.15 / 3.17±1.09		144.81±8.47 / 143.72±8.07		5.40±2.46 / 4.83±1.28	
Visit 2	113.90±8.20 / 113.58±8.83		3.24±0.84 / 3.0±0.92		142.58±10.91 /142.81±10.29		5.25±2.37 / 5.19±2.32	
F Value for eyes	0.89		0.64		0.22		0.05	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS
F Value for visits	3.35		0.06		0.81		2.00	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS
F Value for Interaction	1.10		0.59		1.10		0.40	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS

TABLE 5.39 Giving means ±1SD for the P_2 and CII components and N_2P_2 and CI CII configurations for pattern reversal and pattern onset-offset blue/yellow stimulation respectively in 9 alcoholic subjects who have been repeated.

No. of Visit	CII (ms)		CI CII (uV)		CII (ms)		CI CII (uV)	
	R	L	R	L	R	L	R	L
Visit 1	114.06±7.83 / 113.61±6.34		5.48±2.42 / 5.62±2.64		132.64±13.11 / 132.42±13.04		5.55±3.07 / 6.27±6.21	
Visit 2	113.31±7.85 /113.86±6.81		4.95±1.88 / 5.56±2.47		127.50±9.62 / 130.33±13.35		5.27±2.15 / 4.34±1.56	
F value for eyes	3.86×10^{-3}		3.16		0.75		0.03	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS
F value for visits	0.02		0.07		3.35		0.73	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS
F value for interaction	0.35		1.27		2.87		1.26	
DF	1,8	NS	1,8	NS	1,8	NS	1,8	NS

TABLE 5.40 Giving means ± 1SD for the CII and CI CII configuration for pattern onset-offset, black/white stimulation ($\overline{56}$' and 14') in 9 alcoholic subjects who have been repeated.

No. of Visit	CII (ms) R	CII (ms) L	CI CII (uV) R	CI CII (uV) L	CII (ms) R	CII (ms) L	CI CII (uV) R	CI CII (uV) L
Visit 1	137.17±12.39 / 140.19±13.18		5.68±3.68 / 5.84±3.18		149.22±11.70 / 149.92±12.12		6.21±3.39 / 6.70±3.61	
Visit 2	133.97±6.72 /135.24±6.92		6.48±2.02 / 6.45±2.01		144.94±9.77 / 148.06±11.03		5.99±2.07 / 6.03±2.39	
F value for eyes DF	4.12 1,8	NS	0.05 1,8	NS	0.98 1,8	NS	2.32 1,8	NS
F value for visits DF	1.74 1,8	NS	0.33 1,8	NS	4.71 1,8	NS	0.21 1,8	NS
F value interaction DF	0.91 1,8	NS	0.35 1,8	NS	1.43 1,8	NS	17.04 1,8	p<0.01

TABLE 5.41 Giving means ± 1SD for the CII component and CI CII configuration for pattern onset-offset red/green stimulation (56' and 14') in 9 alcoholic subjects who have been repeated.

(Figure 5.13). This difference in performance between the two eyes is also reflected in the VAs of this patient (Table 5.27).

5.2.2 Psychophysical Results

Visual Fields

The levels of significance for the macular thresholds between alcoholics and controls, to red, green and white stimulation are 1%. 5% and 5% respectively for each eye. The results for blue stimulation and for the visual field scores are not significant (Table 5.42). These findings are in agreement with those reported by Bhargava and Phillips (1974) for the foveal thresholds in tobacco amblyopes for red, green and blue light.

The results for the initial and repeat investigations do not reveal any significant differences (Table 5.43).

The Fusion Thresholds to Flicker Stimulation at 3, 10 and 30 Hz

Significantly differing results between alcoholics and controls have been obtained at the flicker frequencies of 3 and 10 Hz, with a higher significance for the latter frequency ($p<0.05$ and $p<0.01$ respectively, Table 5.44). This result would suggest that it is the tonic rather than the phasic cells which are more affected, although the tonic long and middle wavelength sensitive cones can have relatively high flicker fusion frequencies, as well as there are a few phasic cells which have low flicker fusion frequencies, (Gouras and Zrenner, 1979; Gouras-personal communication).

Subject Group	MACULAR THRESHOLD (log units)								Visual Field Score (log units)	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L	R	L
1	2.6+0.15/2.6+0.14 (2.4-2.8)(2.4-2.8)		2.35+ 0.23/2.36+0.19 (1.6-2.6) (2.0-2.6)		1.74+0.25/1.74+0.21 (1.2-2.0) (1.4-2.0)		1.01+0.19/1.02+0.14 (0.8-1.2) (0.4-1.4)		223.03±19.02/223.29±19.06	
2	2.71+0.10/2.70+0.10 (2.6-2.8) (2.6-2.8)		2.50+0.16/2.52+0.12 (2.2-2.8) (2.2-2.6)		1.43+0.21/1.92+0.19 (1.6-2.2) (1.6-2.2)		1.02+0.18/1.04+0.19 (0.8-1.4) (0.8-1.4)		230.15±12.17/230.81±12.96	
Non zero Value (n)	12	12	14	14	17	17	14	15	20	20
T Value for R & L eyes Between Groups	8.5	8	17	15	23	17	51.5	45.5	92.5	89.5
	p<0.05	p<0.05	p<0.05	p<0.05	p<0.01	p<0.01	NS	NS	NS	NS
Non zero Value (n)	6		7		3		3		19	
T Value for Interocular Difference	9.5		12		1		3		94	
	NS		NS		Unspecified		Unspecified		NS	

Key: 1: Alcoholic Subjects 2: Control Subjects.

TABLE 5.42 Giving (means ± 1SD) and ranges of the macular threshold measurements and the means ± 1 SD for the visual field scores in 21 alcoholic and 21 control subjects.

No. of Visit	MACULAR THRESHOLD (log units)								Visual Field Score (log units)	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L	R	L
Visit 1	2.6±0.09/2.59±0.13 (2.4-2.8)	(2.4-2.8)	2.44±0.13/2.42±0.11 (2.2-2.6)	(2.2-2.6)	1.86±0.16/1.85±0.20 (1.6-2.0)	(1.6-2.0)	1.04±0.23/1.05±0.20 (0.6-1.4)	(0.8-1.4)	223.94±9.89/224.78±10.50	
Visit 2	2.58±0.11/2.59±0.16 (2.4-2.8)	(2.4-2.8)	2.36±0.16/2.40±0.12 (2.0-2.6)	(2.2-2.6)	1.86±0.16/1.85±0.17 (1.6-2.0)	(1.0-2.0)	1.08±0.19/1.06±0.18 (0.8-1.4)	(0.8-1.4)	223.50±10.05/225.82±11.20	
Non zero Value (n)	3	4	6	8	5	5	3	2	10	12
T value for R&L eyes between visits.	0	1	1.5	3	0	0	1	1	14.5	15
	Unspecified		NS	NS	NS	NS	Unspecified		NS	NS

TABLE 5.43 Giving (means ± 1 SD) and ranges for the macular thresholds; the means ± 1SD for the visual field scores in 10 alcoholic subjects who have been repeated.

LOG SENSITIVITY (log units)

Subject Group	3Hz R	3Hz L	10 Hz R	10 Hz L	30 Hz R	30 Hz L
1	1.6552±0.1144/1.6485±0.1029		1.7948±0.0788/1.7636±0.0687		1.0910±0.1647/1.0729±0.1546	
2	1.7168±0.0763/1.7046±0.0774		1.8479±0.0947/1.8381±0.0932		1.0866±0.225±1.0946±0.2124	
F Value for Eyes	4.33		4.20		0.42	
DF	1.20	NS	1.20	NS	1.20	NS
F Value for Groups	4.78		9.10		0.03	
DF	1.20	$p \leq 0.05$	1.20	$p < 0.01$	1.20	NS
F Value for Interaction	0.17		1.00		1.56	
DF	1.20	NS	1.20	NS	1.20	NS

Key: 1: Alcoholic Subjects 2: Control Subjects

TABLE 5.44 Giving the means ± 1 SD for the log sensitivities of the flicker fusion thresholds in 21 alcoholic and 21 control subjects.

However, on considering the retinal region being stimulated (central 2^{o}) it would seem that the tonic cells are more vulnerable.

On the repeat study, a significant increase in log sensitivity is seen at 3 Hz ($p<0.05$, Table 5.45) which would indicate improved function in the cones with low fusion frequencies (possibly the short wavelength sensitive cones).

The H-R-R pseudoisochromatic plate test has not revealed any marked abnormalities except in subject 20 who showed a mild deuteranopic defect. This patient did not return for a repeat investigation to see if this slight defect improved. This result would suggest that any abnormalities seen to colour stimulation on the other tests are not of a congenital nature. It should also be mentioned that no marked interocular differences have been obtained in the statistical analysis for any of the tests used on these patients.

Although significantly different results have been observed between alcoholic and control subjects, the tests on which abnormal results (that is, two standard deviations above or below the normal mean for the age, see appendix 9), have been obtained are:-

Electroretinograms

1) photopic OPs (3 subjects - 14, 15, 20).

LOG SENSITIVITY (log units)

No. of Visit	3Hz R	3Hz L	10Hz R	10Hz L	30Hz R	30Hz L
Visit 1	1.5899±0.1147 / 1.6023±0.1114		1.7689±0.0890 / 1.7637±0.0802		1.0325±0.1000 / 1.0018±0.0890	
Visit 2	1.7112±0.0897 / 1.6712±0.1014		1.8196±0.1508 / 1.8005±0.1252		0.9782±0.1394 / 0.9820±0.1461	
F value for eyes DF	1.82 1,9	NS	1.79 1,9	NS	2.87 1,9	NS
F value for visits DF	10.6 1,9	$p<0.05$	1.90 1,9	NS	1.05 1,9	NS
F value for interaction DF	3.89 1,9	NS	0.52 1,9	NS	4.54 1,9	NS

TABLE 5.45 Giving means ± 1 SD for the log sensitivities for flicker fusion in 10 alcoholic subjects who have been repeated.

Visual Evoked Responses

2) Flash P_2 latency (1 subject - 21).

3) Pattern reversal 56' black/white P_2 latency (1 subject - 20 in one eye only).

4) pattern reversal 56' red/green P_2 latency (3 subjects - 6, 16, 20).

5) pattern reversal 56' blue/yellow P_2 latency (4 subjects - 6, 10, 20, 21)

6) pattern reversal 14' black/white P_2 latency (3 subjects - 14, 20, 21)

7) pattern reversal 14' red/green P_2 latency (7 subjects - 6, 10, 14, 15, 16, 20, 21).

8) pattern onset-offset 56' red/green CII latency (4 subjects - 6, 14, 20, 21)

9) pattern onset-offset 56' blue/yellow CII latency (4 subjects - 6, 14, 20, 21)

10) pattern onset-offset 14' black/white CII latency (3 subjects - 14, 20, 21)

11) pattern onset-offset 14' red/green CII latency (6 subjects - 6, 10, 14, 15, 20, 21)

Visual Fields

12) visual field scores (1 subject - 12)

13) red macular threshold (4 subjects - 15, 17, 20, 21)

14) greenmacular threshold (3 subjects - 15, 20, 21)

15) blue macular threshold (2 subjects - 15, 21)

Flicker Fusion Thresholds

16) 3Hz (1 subject - 10)

17) 10 Hz (1 subject - 10)

From the above list, it can be seen that the response to pattern reversal and pattern onset-offset 14' red/green stimulation have produced the largest number of abnormal results within this alcoholic population. It is also to be noted that it is very nearly the same subjects who have demonstrated abnormal responses on both types of stimulation. With the exception of subjects (6, 14, 21), the distance and near VAs of the other four subjects (10, 15, 16, 20) are at least 6/6 and N5 respectively, in each eye. Subjects 6, 14, have visual acutities of at least 6/9 and N6 in each eye whilst subject 21 has approximately a three-line difference in VA between the two eyes (right better than left), (Table 5.27). Therefore, the detection of subclinical changes by the VERs of small check and field sizes, has not been seen to be effectively reflected by the assessment of VA.

It is perhaps not surprising that it is the VER to red/green stimulation which has been mostly affected, as various workers have long reported a reduction in red/green discrimination in chronic alcoholics and tobacco-alcohol amblyopes (especially as being one of the first signs of the latter condition) (Galezowski, 1883; Uthoff, 1886; Chisholm, et al. 1970; Ainley, 1970; Bhargarva, 1973; Sakuma, 1973; Bhargarva and Phillips, 1974; Verriest et al. 1980). It would also appear that the macular region is initially affected more severely than the more peripheral regions.

As some of the alcoholic subjects were receiving medication when they were tested, the possible side effects of these drugs on the eye have to be considered. They are as follows:-

Drug Name	Possible Ocular Side Effects (Taken from O'Connor, Davies, 1976; Martindale, 1977).
1. Epilim (Sodium Valproate)	- none reported
2. Valium	- blurred vision (resulting from mild accommodative disturbance).
3. Librium	- blurred vision (resulting from mild accommodative disturbance)
4. Motival	- blurred vision
5. Epanutin	- blurred vision, diplopia, nystagmus, ptosis and ocular pain.
6. Phenobarbitone	- blurred vision (resulting from accommodative disturbance), diplopia, mydriasis or miosis
7. Pyridostigmine	- miosis, spasm of accommodation
8. Heminevrin	- none reported.
9. Ospolot	- none reported.
10. Glibenclamide	- none reported.
11. Glucophage	- none reported.

As the VER has produced the most abnormal results in this study, the effects of the above drugs on this test will be considered. For flash stimulation, Valium was reported to give rise to a slight but significant increase in both the P_2 latency and N_2P_2 amplitude (Holder, 1973). Since Librium belongs to the same drug group as Valium, it is possible that it has a similar effect upon the VER. Quinalbarbitone which is a member of the barbiturate drug group to which Phenobarbitone also belongs, was not found to produce marked changes upon the VER. (Holder, 1973). It should be mentioned that all of the above studies have been performed on normal subjects and the influence of alcohol could alter the side effects of the drugs upon the VER. The effect of Epilim on the VER of patients suffering

from photosensitive epilepsy was investigated using flash and flashed-pattern stimulation. It was found that there were no significant changes in the P_2 latency, however, there was a decrease in the amplitude of the N_2P_2 configuration in relation to pre-drug levels (Herrick and Harding 1980). The effects of the other drugs upon the VER have not been reported to the best knowledge of the author.

On considering the alcoholic patients who were taking medication, it has been observed that the three subjects (5, 9, 18) who were receiving Epilim, Motival and Librium respectively, have not revealed abnormal results in any of the tests. Although subject 6 has demonstrated delayed and absent VERs, it would appear as if the effect of Valium has been negligible as the VER results are very similar for the first and second investigations, whereby on the first investigation, Valium was being administered whilst on the second investigation, it had been stopped five weeks prior to testing. It is not possible to say whether Heminevrin (which is structurally on its own - Watson personal communication) has influenced the results of subjects 14, 21. However, it does not seem as if the drugs, Glibencamide and Glucophage had a significant effect upon the VERs of the latter subject (21), as his responses improved on the second investigation whilst he was still on these drugs (Figure 5.13 ~~5.12~~). The possible side effects of Pyridostigmine on the abnormal results of subject 15 and Phenobarbitone, Epanutin, and Ospolot on the results of subject 10 cannot be disregarded.

5.2.3. General Discussion and Summary of Findings

The overall results of the visual field and VER investigations show similar tendencies and therefore agree fairly well. That is, the macular thresholds demonstrate reduced sensitivity to red, green and white lights (especially to red), which is also reflected in the VER to red/green stimulation of the smaller check and field size. The higher significance level observed for 14' black/white VER stimulation than for the white macular threshold could be because of the added effect of contour of the former type of stimulation and also the difference in the frequency of stimulation (the duration of flash on the visual field analyser is only 0.3 ms and therefore would stimulate high frequency sensitivity as opposed to the low frequency for VER stimulation). The summed visual field scores to white stimulation have not revealed a significant difference however, the results to flash VER stimulation are significant ($p<0.05$). Harding (personal communication) explained the effectiveness of flash stimulation as being due to its ability to activate many neurones, that is, it "floods" the system.

The flicker fusion log sensitivities reveal a depression for the lower frequencies, more so to 10 Hz than to 3 Hz. Therefore it would appear that the cells in the macular region with lower flicker fusion frequencies are more affected which indicate the tonic cells. On the repeat investigation, a significant improvement in sensitivity is obtained at 3Hz. This would suggest an increase in sensitivity in the lower frequency flicker sensitive cones.

The alcoholic subjects have been found to have significantly larger pupil sizes than the control subjects ($p<0.05$; $t = 2.383$). However, the effect of increased pupil size would have produced a reduction in the peak latencies of the VERs and an improvement in the macular threshold. This is opposite to the results which have been obtained, therefore indicating that there is a genuine deterioration in the visual system of the alcoholics.

In conclusion, the results obtained from the chronic alcoholics indicate that the visual function of both the retina and the higher visual pathways have been affected. The changes in visual function produce a reduction in sensitivity primarily in the macular region, especially to red stimulation. The larger number of abnormal data observed for pattern VER stimulation than for ERG stimulation could be indicative of initial visual changes occurring behind the inner layers of the retina. However, as these visual changes are more evident in the macular region, it is possible that these results could be partly influenced by the greater sensitivity of the pattern VER (due to the nature of the test) in comparison to the ERG, to changes in the macular representation of the visual pathway.

Out of all the tests used in this study, the VER is the most effective in detecting subclinical changes. This supports the findings of various workers who have compared psychophysical and VER results in toxic and non-toxic conditions (Halliday, 1976; Foulds, 1981; Harding et al. 1982). Six of the seven subjects who have yielded abnormal responses to pattern red/green stimulation of the smaller check size, have demonstrated satisfactory VAs. On calculating

correlation coefficients between the tests which have produced the most significant results, only weak, if any correlations have been found (pattern reversal 14' black/white P_2 latency versus red macular thresholds, -0.2837; pattern reversal 14' black/white P_2 latency versus flicker 10 Hz stimuation -1.0015×10^{-2}; red macular threshold versus flicker 10 Hz stimulation, -0.1123). This result could be accounted for by the fact that with the exception of the VER investigation only a few subjects have demonstrated abnormal values on the other tests. However, these values of the other tests have a consistent tendency to be worse than those of the control subjects and therefore give rise to significantly different results.

The seven patients (6, 10, 14, 15, 16, 20, 21) who have demonstrated abnormal VERs, nearly all have long drinking histories (with the exception of subject 15 who is female), although there are other subjects with long drinking histories who have not been affected. With the exception of one patient (21) who is a non-smoker, the other affected patients smoke between 15-50 cigarettes per day, including rolling tobacco. Only one patient (11) in the study, smoked pipe tobacco. It is interesting to note that the 3 patients (16, 20, 21) who either have liver damage or enlargement of the liver have shown VER changes with one of them having undergone operations for peptic ulcers (subject 20) and another suffering from diabetes (subject 21). It is difficult to assess the alcoholic intake of these patients because of the variable intake in some patients and the difference between the quantities of alcohol which appeared on the hospital records and those which have been given by the patients for this study. However, the majority of these patients have poor appetites and consume combinations of spirits and wine, even surgical and methylated spirits.

5.3 Data for Tobacco-Alcohol Amblyopes

Seven male patients diagnosed as suffering from tobacco-alcohol amblyopia have been examined and their results have been compared to those of 7 age-and-sex matched controls, (Table 5.46). Only 3 of these patients have been repeated after approximately 8 weeks as the others failed to return. On looking at the age of these affected patients, it can be seen that it is fairly advanced ($\bar{x}$ = 56.9 $\pm$9.7 yr) which has been previously reported (Reed and Drance, 1972; Harrington, 1982).

5.3.1 Electrophysiological Results

Electroretinograms

The ERG results have been analysed by two-way ANOVA for related samples. For the dark-adapted and photopic ERGs no marked differences have been obtained for the peak latencies of the A wave and the amplitude of the AB configuration. However, there is a significant difference for the peak latency of the B wave for the dark-adapted ERG ($p < 0.05$, Table 5.47) but not for the photopic ERG. This reduction in the significance levels of the B wave latency in comparison to those for the chronic alcoholics could be due to the small number of subjects, especially since the data for the photopic ERG of one subect, (EH_1) had to be omitted due to a poorly formed response. On inspecting the peak latency values for the dark-adapted B wave, it is observed that they all fell within normal limits for the age.

For the photopic ERG, the second OP is reduced in one subject (AT) and abolished in 2 other subjects (EH_1 and EH_2), whilst the first OP

Subject Age (yr) Sex Diagnosis	Visual Acuity RE/LE 1st Visit RE/LE 2nd Visit	Pupil Size (mm)	Ocular Changes	Smoking habits/ Period of Smoking (yr)	Alcoholic Intake/ Period of Drinking (yr)	Onset of Symptoms prior to 1st Visit Other Illnesses	Period Between Visits	Medication 1st Visit 2nd Visit	Appetite
EH_1 44 M T/A ambly.	6/9- N10 6/9 N10 6/9 N10 6/9 N10	4.5 4.5	NAD	10 panatellas per day. 28	Drinks liberally. 21	3/12	14/52	None	Fair
CJ 46 M T/A ambly.	6/36 N48 6/60<N48 6/36 N48 6/36<N48	4.5 5	Mild diabetic retino-pathy.	28.4 g pipe tobacco/day 23	1.1 l beer/ day 26	11/12 Diabetes	10/52	None/ Vit B_{12} inj for past 4 wks.	Good
EC 52 M T/A ambly.	6/24 N36 6/12+1 N18	4.5	Old chor-oiditis in LE, infer-ior tempor-ally.	25 cig/day + 1 cigar/day 32	6 shorts whiskey + 0.6l beer per day. 20	9/12	FTR	Vit B_{12} inj for 5 wk/ FTR.	Poor
NB 60 M T/A ambly	6/12 N10 6/18+2 N10 6/9 N6 6/12+2 N6 just	5 4.5	NAD	14 g pipe tobacco/day 25	1.7 l beer/ day 35	3 years	20/52	Vit B_{12} inj for 2 yr/Vit B_{12} inj.	Fair
AT 61 M T/A ambly	6/18+2N14 6/18+2 N14	3.5	NAD	40 cig/day until 2 year ago; now smokes 16g pipe tobacco per day. 40	1.7 - 2.2l beer/day	6/12	FTR	None	Fair
JM 66 M T/A + nutritional ambly.	6/36 N24 6/18+1 N18	3	R esot	28.5g pipe tobacco/day 40	5 bot. Guin-ness + 1 bot. beer/day 45	Reduction in VA in LE for 10/12	FTR	None	Poor
EH_2 69 M T/A ambly	3/60<N48 3/36<N48	3.55	Early lens opacities; pale optic discs	57-113.4 g pipe tobacco per week. 38	2.2l beer/ day 40	9/12 Hyper-tension	FTR	Vit B_{12} for 3 wk, Aldomet.	Fair

Key: T/A - Tobacco alcohol amblyopia; S - sluggish; cig - cigarette; tob - tobacco; FTR - failed to return.
R esot - right esotropia

Table 5.46 Giving the particulars of the tobacco alcohol amblyopes.

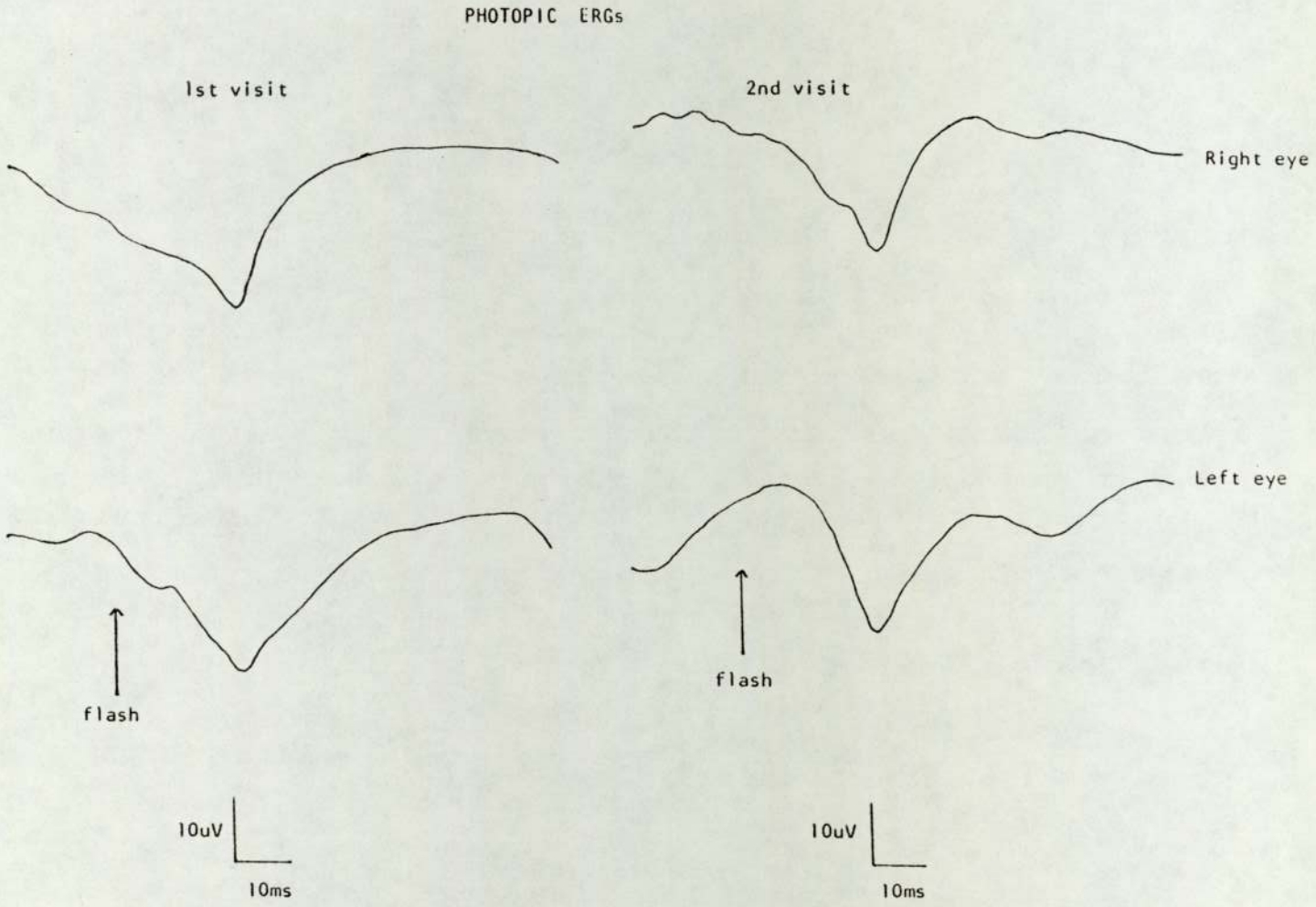
Subject Group	DARK ADAPTED LOW INTENSITY			PHOTOPIC				
	A(ms) R L	B(ms) R L	AB(uV) R L	A(ms) R L	B(ms) R L	OP1(ms) R L	OP2(ms) R L	AB(uV) R L
1	26.82±2.51/ 27.36±2.47	51.71±1.34/ 51.46±1.43	214.46±38.09/ 204.83±26.21	20.86±1.25/ 20.64±0.69	43.50±2.05/ 43.83±2.07	25.42±1.36/ 25.50±1.44 No OP in 1 Subject	No OPs in 3 Subjects.	88.03±25.03/ 94.08±28.84
2	26.39±1.60/ 26.61±1.80	50.11±0.50/ 50.18±0.83	227.37±24.70/ 230.41±19.56	20.79±0.76/ 21.07±0.98	43.17±2.70/ 42.88±2.25	26.08±0.91/ 25.83±1.21	31.93±0.89/ 31.64±0.75	74.95±13.94 81.13±17.44
F Value for Eyes DF	2.72 1,6 NS	0.01 1,6 NS	0.09 1,6 NS	9.87×10^{-3} 1,6 NS	0.01 1,5 NS	0.19 1,5 NS	Not Analysed.	1.78 1,5 NS
F Value for Groups DF	0.82 1,6 NS	10.08 1,6 p<0.05	0.88 1,6 NS	0.25 1,6 NS	0.70 1,5 NS	0.85 1,5 NS	Not Analysed	3.79 1,5 NS
F Value for Interaction DF	0.85 1,6 NS	1.87 1,6 NS	3.32 1,6 NS	0.66 1,6 NS	0.70 1,5 NS	0.57 1,5 NS	Not Analysed	0.86 1,5 NS

Key:- 1 - Tobacco-amblyopes; 2; Control subjects

Table 5.47 Giving the means ± 1SD for the components of the dark-adapted and photopic ERGs in 7 tobacco alcohol amblyopes and 7 control subjects.

is abolished in one subject (EH_1 - the ERG of this subject seems only to contain an A wave) (Figure 5.14).

There have been varied reports on the behaviour of the ERG in tobacco-alcohol amblyopes, in that some workers found no marked changes in the ERG (Kriss et al. 1982) whilst others reported that the photopic system is more affected than the scotopic system (Stangos et al. 1970, 1977; Ikeda et al, 1978; Van Lith and Vijkvinkel-Bruinenga, 1978; Leighton et al 1979). In chronic alcoholics, Cinotti et al (1970) found that the scotopic system is more affected than the photopic system. This variation in the ERG results could be due to the different testing conditions used by various workers and in many studies, only amplitude measures have been made. In this study, it has been found that the most sensitive component of the ERG, is the OP which has been suggested to be linked to photopic activity (Stangos, et al. 1970, 1977; Korth, 1980). The second OP has been more affected than the first one for both the chronic alcoholics and tobacco-alcohol amblyopes. This difference in the behaviour of the OPs has been previously observed by Stangos et al.(1970, 1977) who reported that whereas the first OP might be the most resistant under a particular type of stimulation, it can become the least resistant under another form of stimulation. This independent behaviour of the OPs under different conditions of stimulation and in disease, would suggest different sources of origin. The results of a study performed by Wachmeister and Dowling (1979) on the mudpuppy retina have indicated that the OPs have separate origins as it was found that they independently reversed in polarity at various points across the retina.



EH_1, aged 44 yrs.

Figure 5.14 The photopic ERGs, of a tobacco-alcohol amblyope which did not demonstrate any improvement on the repeat investigation

The ERGs of three subjects (EH_1, CJ, NB) who have been repeated remained very similar in form to those obtained on the first investigation, with the peak latencies being more consistent than the amplitudes (the lowest ratio between the amplitudes of the AB configuration on both occasions is 0.65). The photopic ERG of subject EH_1 failed to improve on the second visit.

Visual Evoked Responses

The peak latencies of the P_2 and CII components have been analysed by using the Fisher-Yates test of significance (Finney, 1948). Non-parametric statistics had to be used instead of the more powerful parametric statistics because many of the VERs are so poorly formed that no latency measures could be made and hence, a quantitative value could not be given. The criterion for abnormality is:- 1) if the latency of the VER lies beyond two standard deviations of the mean value (see appendix 9); or 2) if the responses are indiscernible.

On referring to table 5.48 which presents the results for flash stimulation, it can be seen that a significant difference has not been achieved. However, 3 of the 7 tobacco-alcohol amblyopes (NB, JM, EH_2) demonstrated the PNP complex which has been previously reported in toxic optic neuropathy, hereditary optic atrophy and ischaemic neuropathy, (Harding et al. 1978; Kriss et al. 1982) (Figure 5.15). These three subjects had P_2 latencies which were either at the upper limits of normality or were delayed. Nevertheless, it should be mentioned that these patients were over 60

Type of Stimulus	Right Eye	Control Subject	Tobacco-Alcohol Amblyope	Significance Level	Left Eye	Control Subject	Tobacco-Alcohol Amblyope	Significance
Flash	Normal Abnormal	7 0	5 2	NS	Normal Abnormal	7 0	4 3	NS
PR 56' B/W	Normal Abnormal	7 0	1 6	$p<0.002$	Normal Abnormal	7 0	1 6	$p<0.002$
PR 14' B/W	Normal Abnormal	7 0	1 6	$p<0.002$	Normal Abnormal	7 0	1 6	$p<0.002$
PR 56' R/G	Normal Abnormal	7 0	1 6	$p<0.002$	Normal Abnormal	7 0	1 6	$p<0.002$
PR 14' R/G	Normal Abnormal	7 0	0 7	$p<0.002$	Normal Abnormal	7 0	0 7	$p<0.002$
PR 56' B/Y	Normal Abnormal	7 0	0 7	$p<0.002$	Normal Abnormal	7 0	1 6	$p<0.002$

Key:- PR - Pattern reversal; B/W - Black/White; R/G - Red/Green; B/Y - Blue/Yellow.

TABLE 5.48 Showing the number of P_2 peak latencies which fall within or beyond normal limits for 7 control subjects and 7 tobacco-alcohol amblyopes.

years old, which is the age group when the P_1 component becomes larger in normal subjects. It has been observed in 3 of the 20 normal subjects who were 60 years old and over.

For pattern reversal 56' stimulation, 6 subjects have demonstrated abnormal responses. Three subjects (AT, NB, JM) have delayed responses with one of these subjects showing the PNP response reported by Halliday (1976), whilst the other 3 subjects (CJ, EC, EH_2) have yielded indiscernible responses (Figure 5.15). All the other types of pattern reversal stimulation have given highly significant results ($p<0.002$; Table 5.48).

The results of the amplitudes of the N_2P_2 configuration which have been analysed by two-way ANOVA are shown in Table 5.49, 5.50. For flash stimulation, there is no marked difference between the data for the tobacco-alcohol amblyopes and the control subjects. For pattern reversal 56' stimulation for black/white and blue/yellow stimulation, a 5% level of significance is reached whilst for the other forms of stimulation, a 1% level is obtained.

For the CII component of pattern onset-offset stimulation, the results for 56' black/white stimulation have not attained significance whilst those for the 56' red/green and blue/yellow stimulation have attained a significance level of 5% (Table 5.51). This difference in the level of significance between onset-offset and reversal stimulation is most likely due to the appearance of discernible responses which are within normal limits for onset-offset stimulation in three subjects whereas reversal stimulation shows either delayed

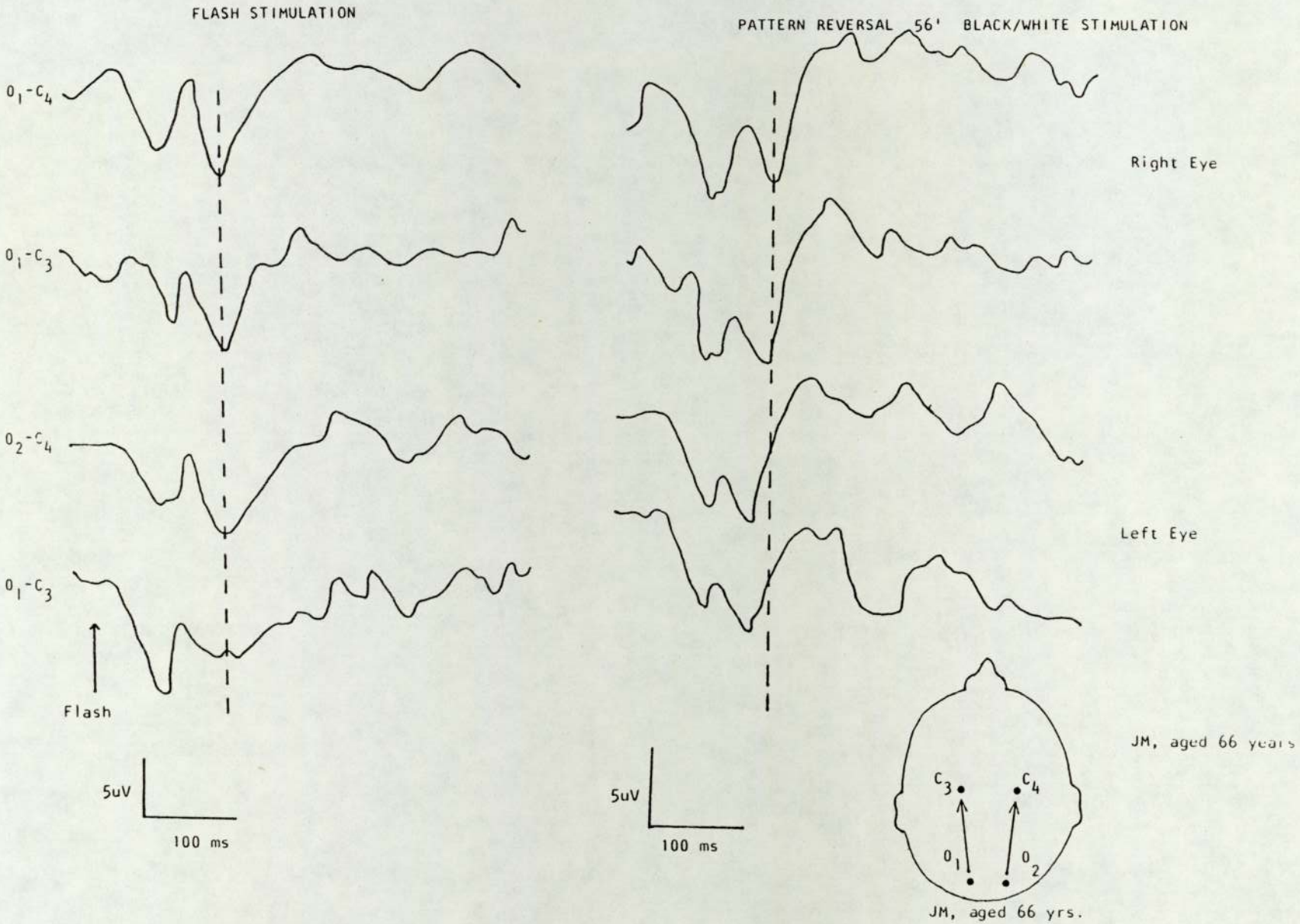


Figure 5.15 The VERs to flash and pattern reversal stimulation which demonstrate the PNP waveform in a tobacco-alcohol amblyope

Subject Grp	PR 56' B/Y		Flash	
	N_2P_2 (uV)		N_2P_2 (uV)	
1	1.10±1.92/1.04±1.97		4.75±3.46/4.83±3.61	
2	3.01±0.92/3.50±1.18		6.69±2.23/7.40±3.74	
F Value for Eyes DF	1.68 1,6	NS	1.86 1,6	NS
F Value for Groups DF	6.01 1,6	$p<0.05$	1.60 1,6	NS
F Value for Interaction DF	2.31 1,6	NS	0.42 1,6	NS

Table 5.49 Giving the means ± 1SD for the amplitude of the N_2P_2 configuration for flash and pattern reversal stimulation in 7 tobacco alcohol amblyopes and 7 control subjects.

Subject Grp	PR 56' B/W	PR 14' B/W	PR 56' R/G	PR 14' R/G
	N_2P_2 (uV)	N_2P_2 (uV)	N_2P_2 (uV)	N_2P_2 (uV)
1	2.40±2.40/2.26±2.23	1.07±1.90/0.38±1.01	2.38±2.75/1.70±1.67	Indiscernible responses for all subjects
2	4.34±1.61/4.04±1.75	4.76±2.43/5.07±2.16	4.00±1.29/4.36±2.91	4.14±1.85/3.50±1.65
F Value for Eyes DF	0.47 1,6 NS	0.15 1,6 NS	0.38 1,6 NS	Not analysed
F Value for Groups DF	8.65 1,6 p<0.05	15.72 1,6 p<0.01	19.87 1,6 p<0.01	Not analysed
F Value for Interaction DF	0.05 1,6 NS	0.79 1,6 NS	0.69 1,6 NS	Not analysed

Key:- PR - Pattern Reversal, B/W - Black/White, R/G - Red/Green, B/Y - Blue/Yellow

Table 5.50 Giving means ± 1SD for the amplitude of the N_2P_2 configuration for pattern reversal stimulation in 7 tobacco alcohol amblyopes and 7 control subjects.

Type of Stimulus	Right Eye	Control Subject	Tobacco-Alcohol Amblyope	Signif-icance Level	Left Eye	Control Subject	Tobacco-Alcohol Amblyope	Signif-icance Level.
P O/N 56' B/W	Normal Abnormal	7 0	4 3	NS	Normal Abnormal	7 0	4 3	NS
P O/N 14' B/W	Normal Abnormal	7 0	1 6	$p<0.002$	Normal Abnormal	7 0	1 6	$p<0.002$
P O/N 56' R/G	Normal Abnormal	7 0	2 5	$p<0.025$	Normal Abnormal	7 0	2 5	$p<0.025$
P O/N 14' R/G	Normal Abnormal	7 0	0 7	$p<0.002$	Normal Abnormal	7 0	0 7	$p<0.002$
P O/N 56' B/Y	Normal Abnormal	7 0	2 5	$p<0.025$	Normal Abnormal	7 0	2 5	$p<0.025$

Key:- P O/N - Pattern onset-offset; B/W - Black/White; R/G - Red/GReen; B/Y - Blue/Yellow.

TABLE 5.51 Showing the number of CII peak latencies which fall within or beyond normal limits for 7 control subjects and 7 tobacco alcohol amblyopes.

or indiscernible responses in the same subjects (Figure 5.16). The appearance of responses within normal limits could be partly due to the larger standard deviations for pattern onset-offset stimulation.

The results for 14' onset-offset stimulation demonstrate, a marked deterioration in comparison to those for 56' stimulation ($p<0.002$; Table 5.51). For 14' pattern onset-offset and reversal stimulation, it is interesting to note that whereas one subject (EH_1) revealed normal responses to black/white stimulation, none of the subjects gave discernible responses for red/green stimulation (Figure 5.17).

The results for the amplitudes of the CI CII configuration are presented in Table 5.52, 5.53. For 56' black/white and blue/yellow stimulation, a significance level of 5% has been obtained whilst for the other forms of stimulation significance is increased to the 1% level.

The VERs of the 3 repeated subjects remained essentially unchanged, in that, subject EH_2 had normal flash VERs and normal VERs for black/white pattern stimulation but delayed and abolished responses for coloured stimulation; subject CJ had normal flash VERs but did not yield any pattern responses for the routine stimulus parameters on both occasions. However, it has been observed that whilst a response could only be obtained for 5° black/white pattern reversal stimulation, a reasonable VER could be obtained for 2° checks for pattern onset-offset stimulation (Figure 5.16). Unlike the former subjects, the

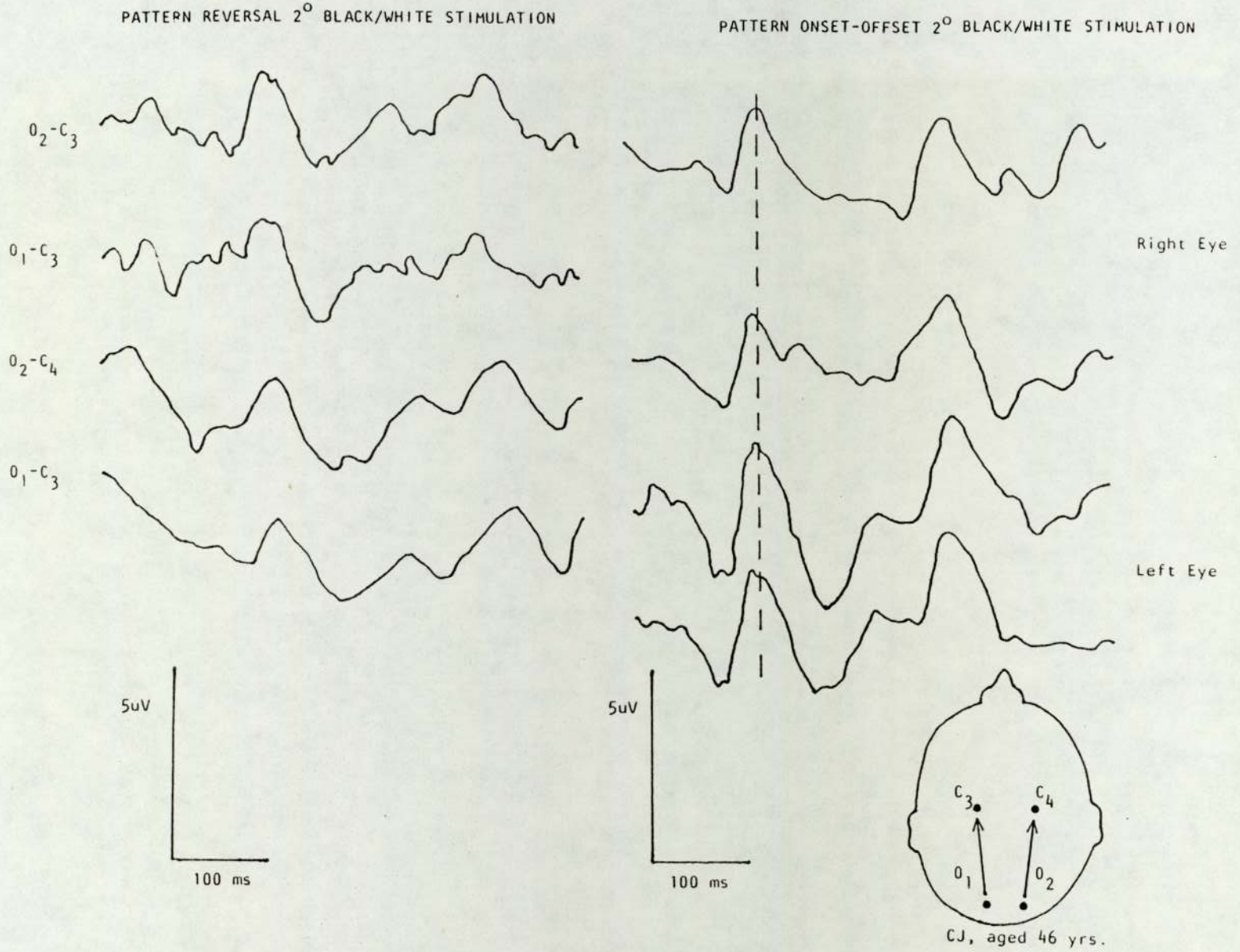


Figure 5.16 The VERs to pattern reversal and pattern onset-offset 2° black/white stimulation in a tobacco-alcohol amblyope whose responses to reversal stimulation were indiscernible whilst those to onset-offset stimulation were within normal limits

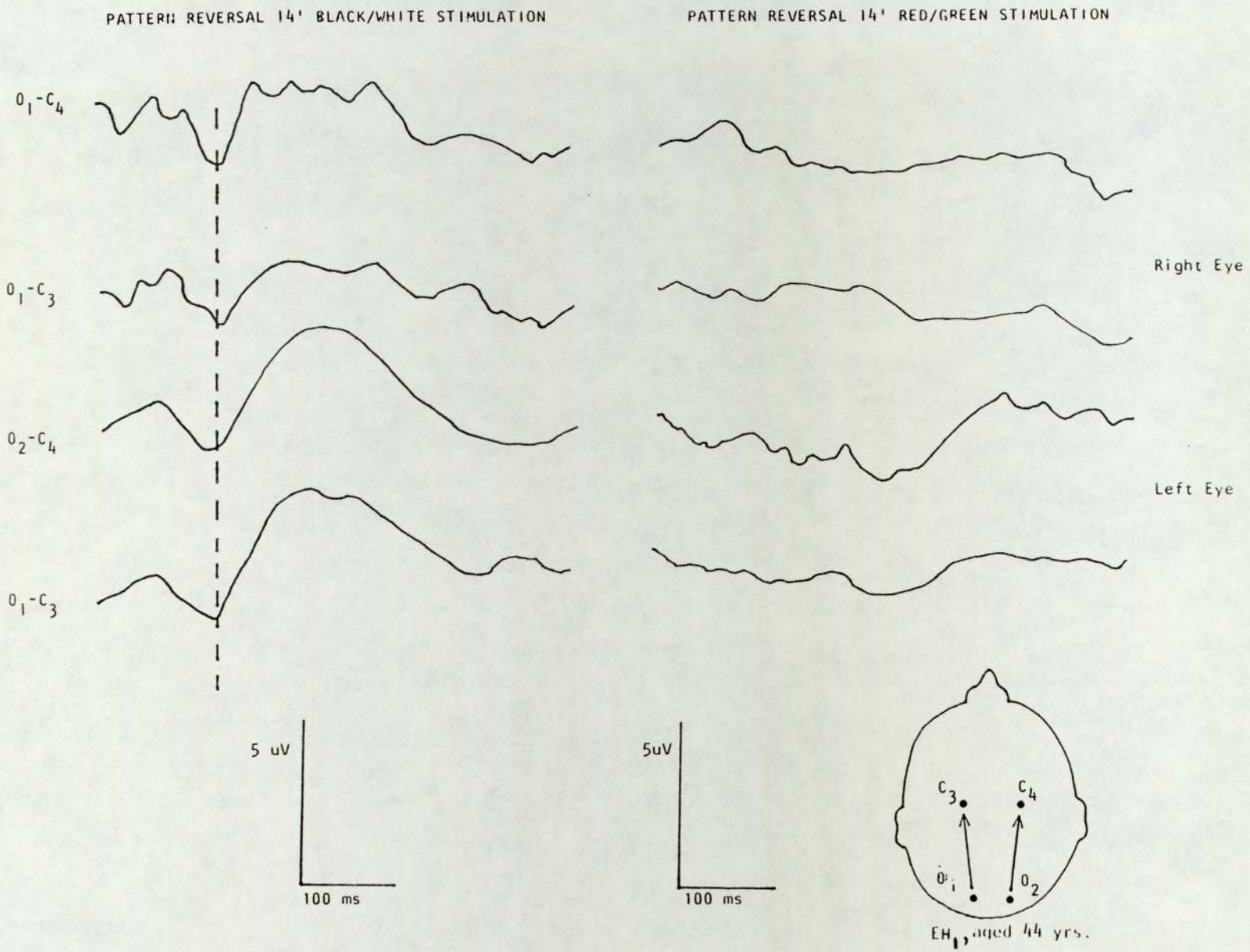


Figure 5.17 The VERs to pattern reversal 14' black/white and red/green stimulation in a tobacco-alcohol amblyope, showing discernible responses to black/white stimulation but indiscernible responses to red/green stimulation

Subject Group	PO/N 56' B/W	PO/N 14' B/W	PO/N 56' R/G	PO/N 14' R/G
	C1 C11 (uV) R L	C1 C11 (uV) R L	C1 C11 (uV) R L	C1 C11 (uV) R L
1	3.63±3.62/3.37±3.25	1.29±2.22/1.05±1.80	2.67±3.41/2.76±2.76	0.79±2.09/0.83±2.18
2	7.12±3.36/7.14±3.45	7.00±1.75/7.76±1.33	7.64±4.02/7.31±3.91	8.12±3.28/8.33±2.93
F Value for Eyes DF	0.14 1,6 NS	1.19 1,6 NS	0.67 1,6 NS	0.14 1,6 NS
F Value for Groups DF	12.91 1,6 p<0.05	86.51 1,6 p<0.01	26.50 1,6 p<0.01	43.65 1,6 p<0.01
F Value for Interaction DF	0.21 1,6 NS	8.05 1,6 p<0.05	1.10 1,6 NS	0.07 1,6 NS

Key: PO/N - Pattern Onset/Offset

Table 5.52 Giving means ± 1 SD for the amplitude of the C1 C11 configuration for pattern onset/offset stimulation in 7 tobacco alcohol amblyopes and 7 control subjects.

Subject Group	PO/N 56' B/Y CI CII (uV) R L
1	1.70±3.27/1.35±3.07
2	5.83±1.31/5.67±2.11
F Value for Eyes DF	0.16 1,6 NS
F Value for Groups DF	6.41 1,6 p<0.05
F Value for Interaction DF	0.09 1,6 NS

Table 5.53 Giving means ± 1SD for the amplitude of the CI CII configuration for blue/yellow 56' pattern onset/offset stimulation in 7 tobacco alcohol amblyopes and 7 control subjects

third subject (NB) demonstrated abnormal flash responses (a delayed PNP complex in the right eye and an indiscernible response in the left eye) and delayed and abolished VERs to pattern stimulation, with the exception of 56' black/white pattern onset-offset stimulation for which he yielded normal VERs.

5.3.2 Psychophysical Results

Visual Fields

The macular thresholds for red, green and white light are all significantly different from those of the controls at the 5% level (no "T" values have been given at the 1% level on the Wilcoxon table). The macular thresholds for blue light have not been analysed as 4 patients did not perceive the light at all (Table 5.54). On comparing the macular thresholds for the right and left eyes of the tobacco-alcohol amblyopes to the range of macular thresholds for normal subjects, of the appropriate age group, the number of patients whose thresholds fall below normal limits are shown in Table 5.55.

Colour of Stimulus	Right Eye	Left Eye
Red	6	6
Green	6	6
Blue	7	6
White	6	5

Table 5.55 Showing the number of tobacco-alcohol amblyopes whose macular thresholds are below the normal range for the age.

The visual field scores are also significantly different from those of the control subjects ($p<0.05$; no "T" values given at the

Subject Groups	MACULAR THRESHOLDS (log units)								Visual Field Score (log units)	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L		
1	1.30±0.68/1.26±0.67 (NS-20) (0.4-2.2)		1.13±0.70/1.20±0.66 One Subject Did Not Perceive Light (NS-2.2) (NS-2.2)		0.67±0.47/0.77±0.37 (NS-1.2) (NS-1.2)		4 subjects did not perceive light. (NS-0.6) (NS-0.8)		162.06±43.00/163.97±41.16	
2	2.51±0.20/2.51±0.20 (2.2-2.8) (2.2-2.8)		2.23±0.24/2.23±0.27 (1.8-2.6) (1.8-2.6)		1.71±0.25/1.71±0.23 (1.4-2.2) (1.2-2.0)		0.83±0.21/0.86±0.25 (0.4-1.0) (0.4-1.2)		201.11±24.32/201.31±24.68	
Non zero value(n)	6	7	6	6	6	6	Not analysed		7	7
T Value for R+L eyes Between Groups.	0	0	0	0	0	0			0	0
	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05	p<0.05			p<0.05	p<0.05
Non zero value (n)	5		3		2				6	
T Value for Interocular difference for Group 1	4		1		0				7	
	NS		Unspecified		Unspecified				NS	

Key: 1 - tobacco-alcohol amblyopes, 2 - control subjects, NS - not seen.

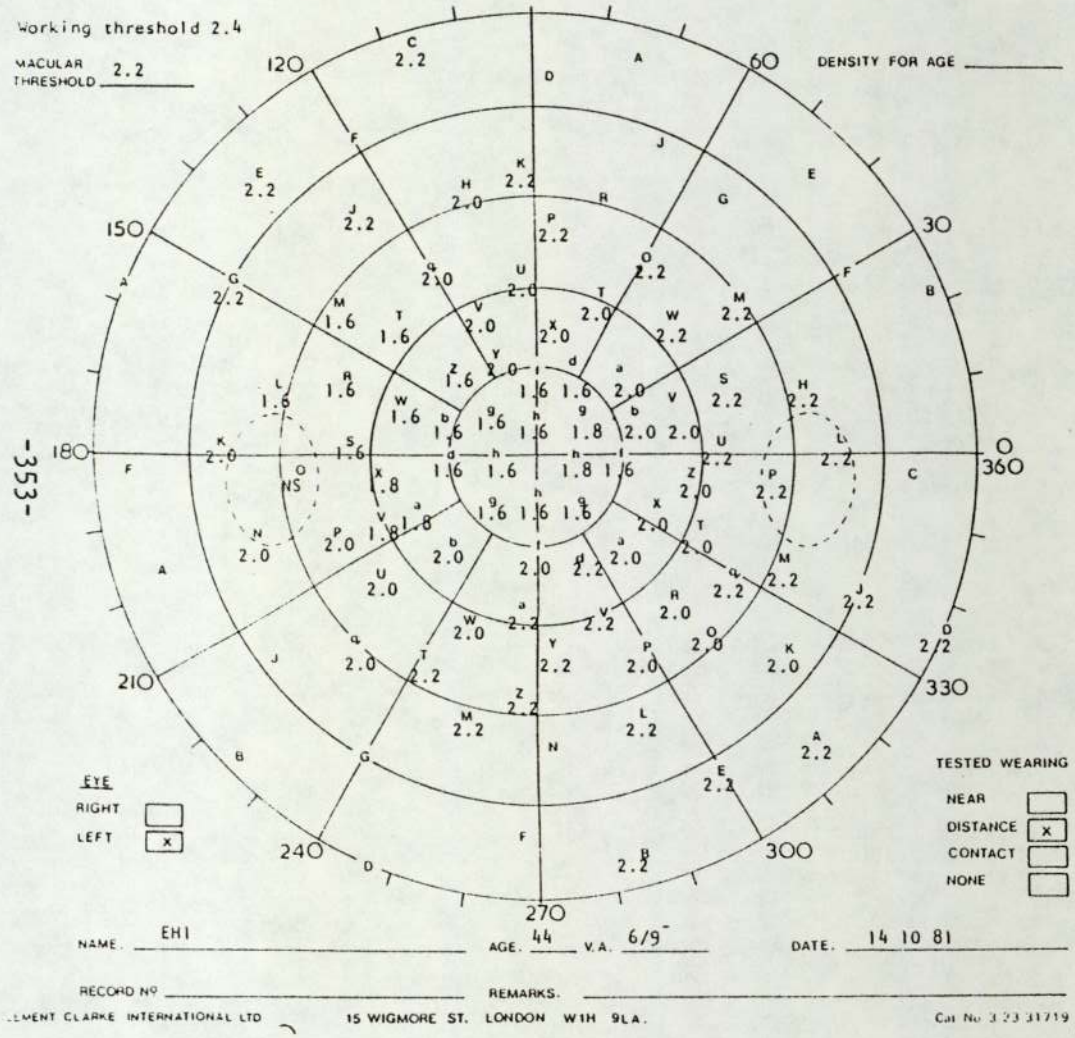
Table 5.54 Giving (means ± 1SD) and ranges of the macular thresholds and the visual field scores in 7 tobacco-alcohol amblyopes and 7 control subjects.

1% level). The visual field charts for 2 subjects (subject EH_1, with the best VA and subject EH_2 with the worst VA) are shown in Figure 5.18, 5.19). For both subjects, the maximum depression in sensitivity is seen in the central and centro-caecal regions, although it is seen to involve the whole visual field (25^{o}) in subject EH_2. In subject EH_1, if the recommended age filter was used to examine his visual fields, then the reduction in sensitivity in comparison to the rest of the visual field would not have been suspected.

For the 3 subjects who have been repeated there is some improvement in the white macular threshold for each eye in all of these subjects. (EH_1 - 0.2 log units; NB - 0.2 log units; CJ - 0.4 log units for the right eye and 0.2 log units for the left eye), which is also accompanied by some increase in sensitivity for the white visual field scores. (Figure 5.20). However, there is no noticeable change for the macular thresholds to coloured stimulation.

The Fusion Thresholds to Flicker Stimulation at 3, 10 and 30Hz.

The results for the flicker fusion log sensitivities have demonstrated significantly different results at 3 and 10 Hz ($p<0.01$). (Table 5.56). However, at 30Hz, 3 subjects were unable to detect flicker at the maximum contrast level (CJ, JM, EH_2) and the results of another subject (AT) were dubious. At this frequency, subject EH_1 could not detect flicker in the right eye only. Hence, the data at 30Hz could not be analysed statistically. These subjects all demonstrated decreased CFF values at the maximum contrast, that is, 15,14,12, 29 and 25 Hz respectively for the right eye. (Figure 5.21).



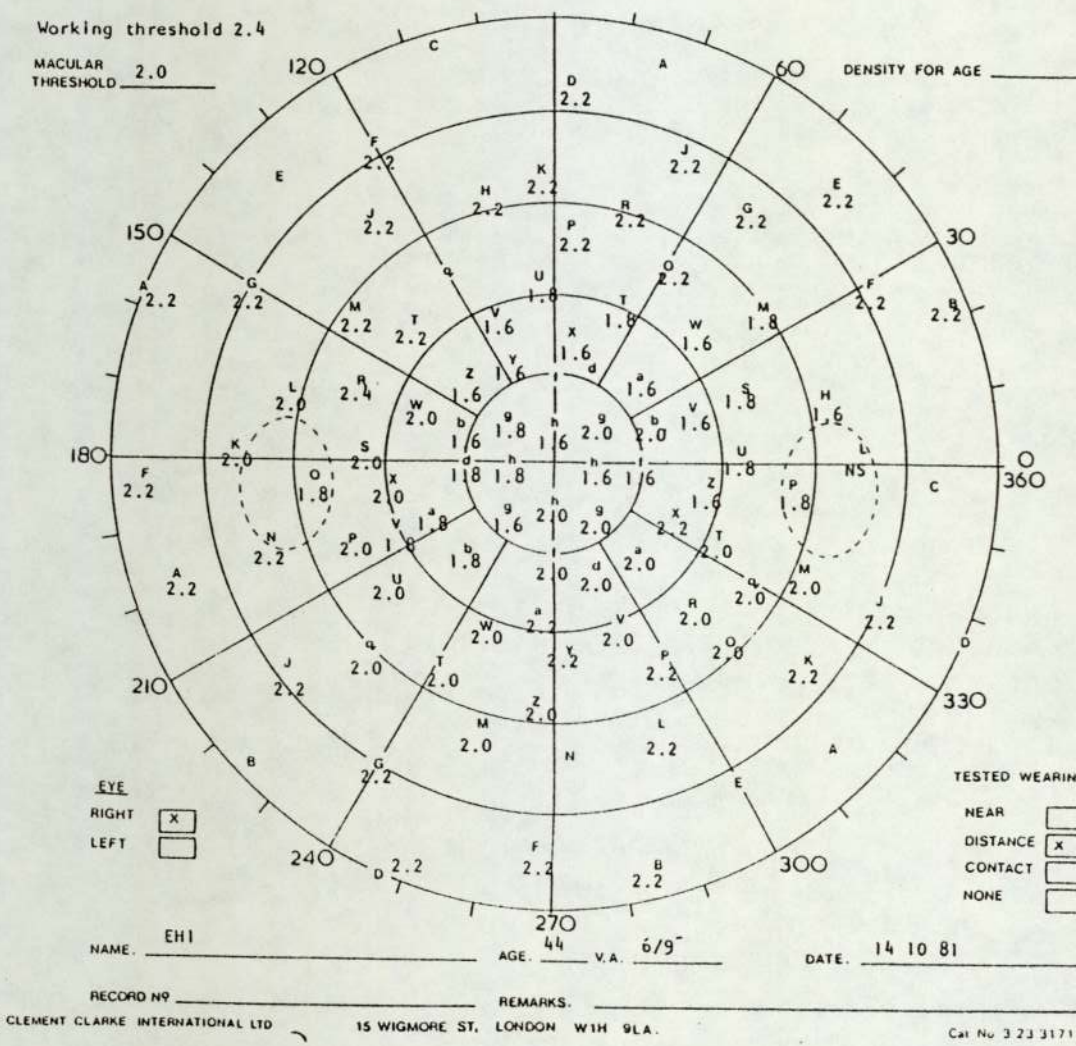


Figure 5.18

The Friedmann visual field plots of a tobacco-alcohol amblyope on the initial investigation, showing some reduction in sensitivity in the central and centrocaecal areas in comparison to the remainder of the visual field

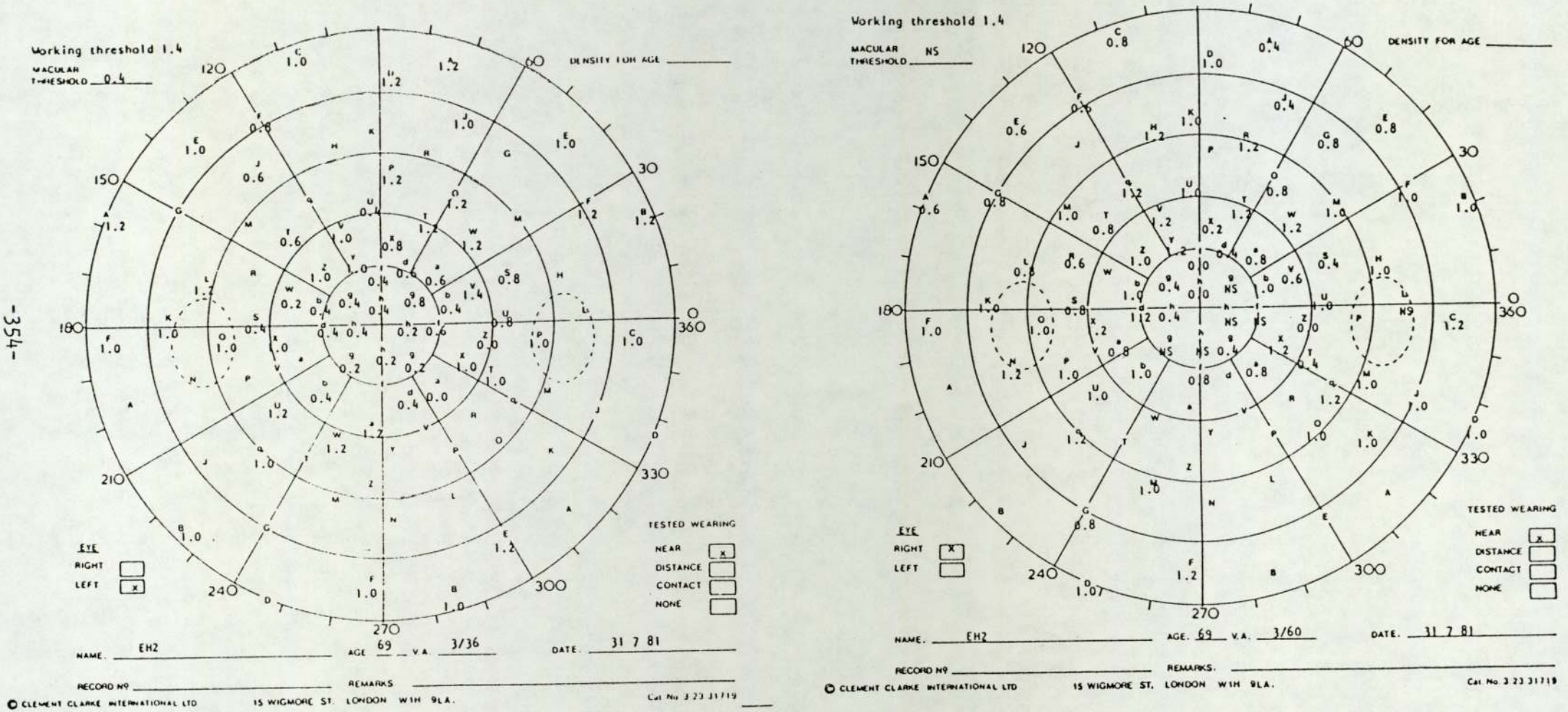
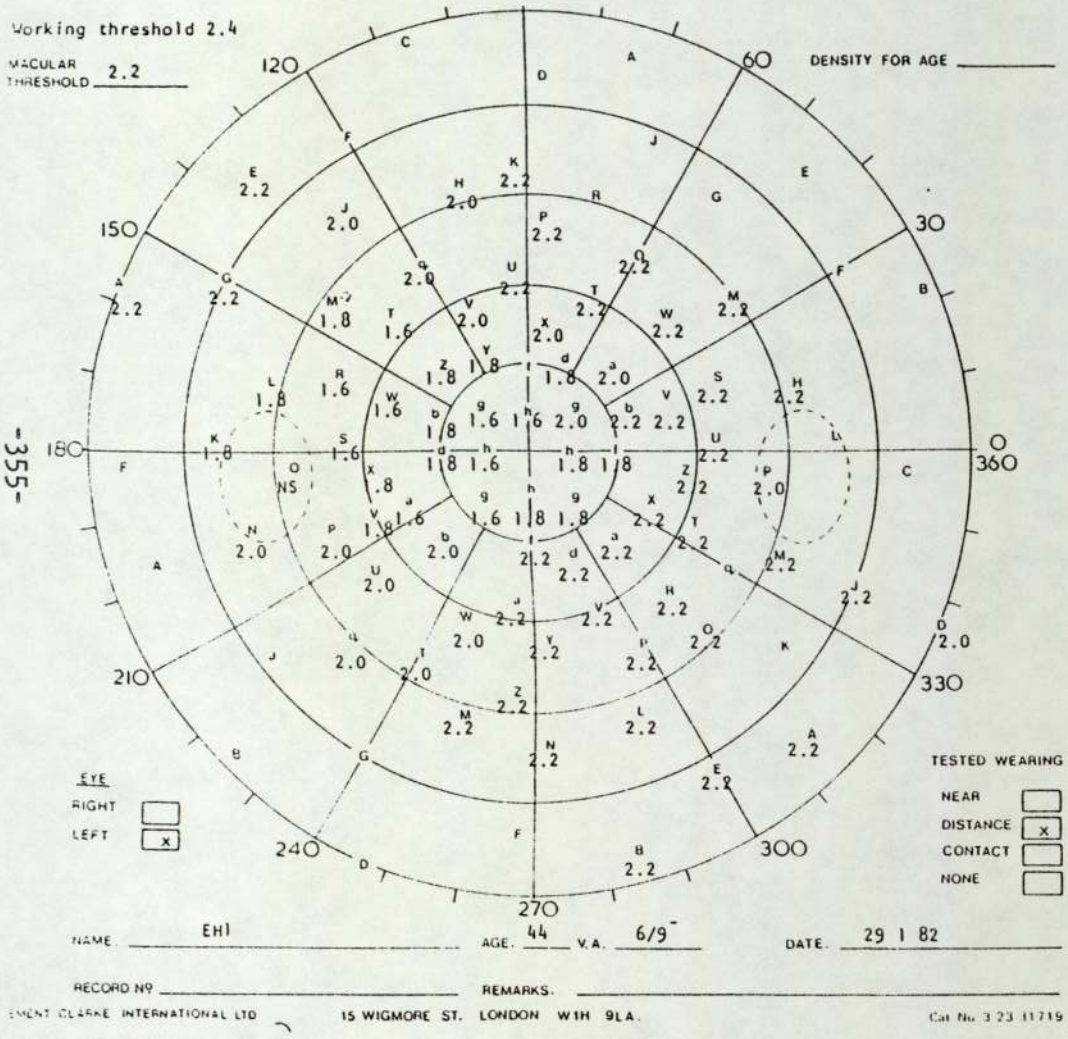


Figure 5.19 The Friedmann visual field plots of a tobacco-alcohol amblyope, on the initial investigation, showing reduced sensitivity in each eye (especially in the ~~left~~ right eye) particularly in the central 10°.



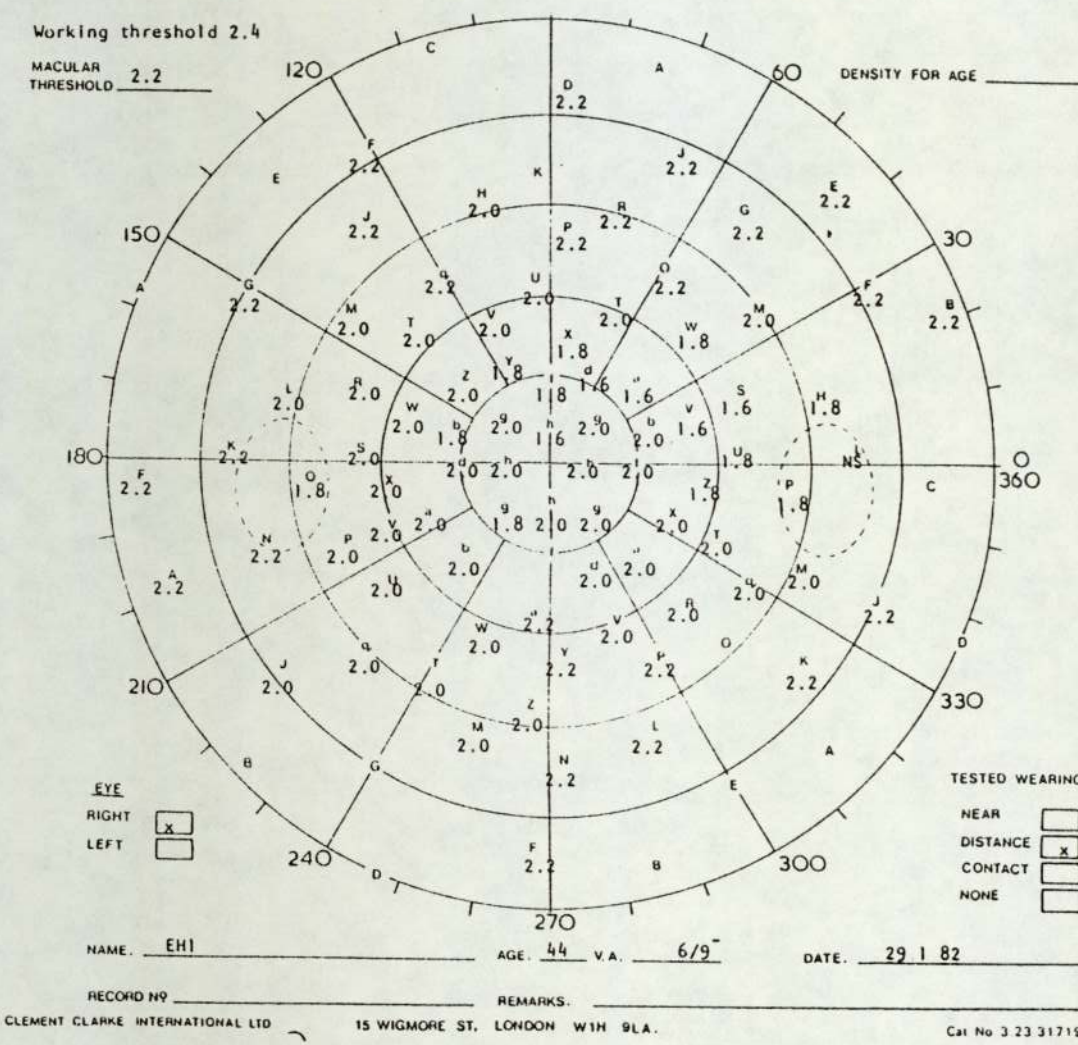


Figure 5.20

The Friedmann visual field plots of the same subject in Figure 5.18. It can be seen that there is an improvement in sensitivity within the central and centrocaecal areas

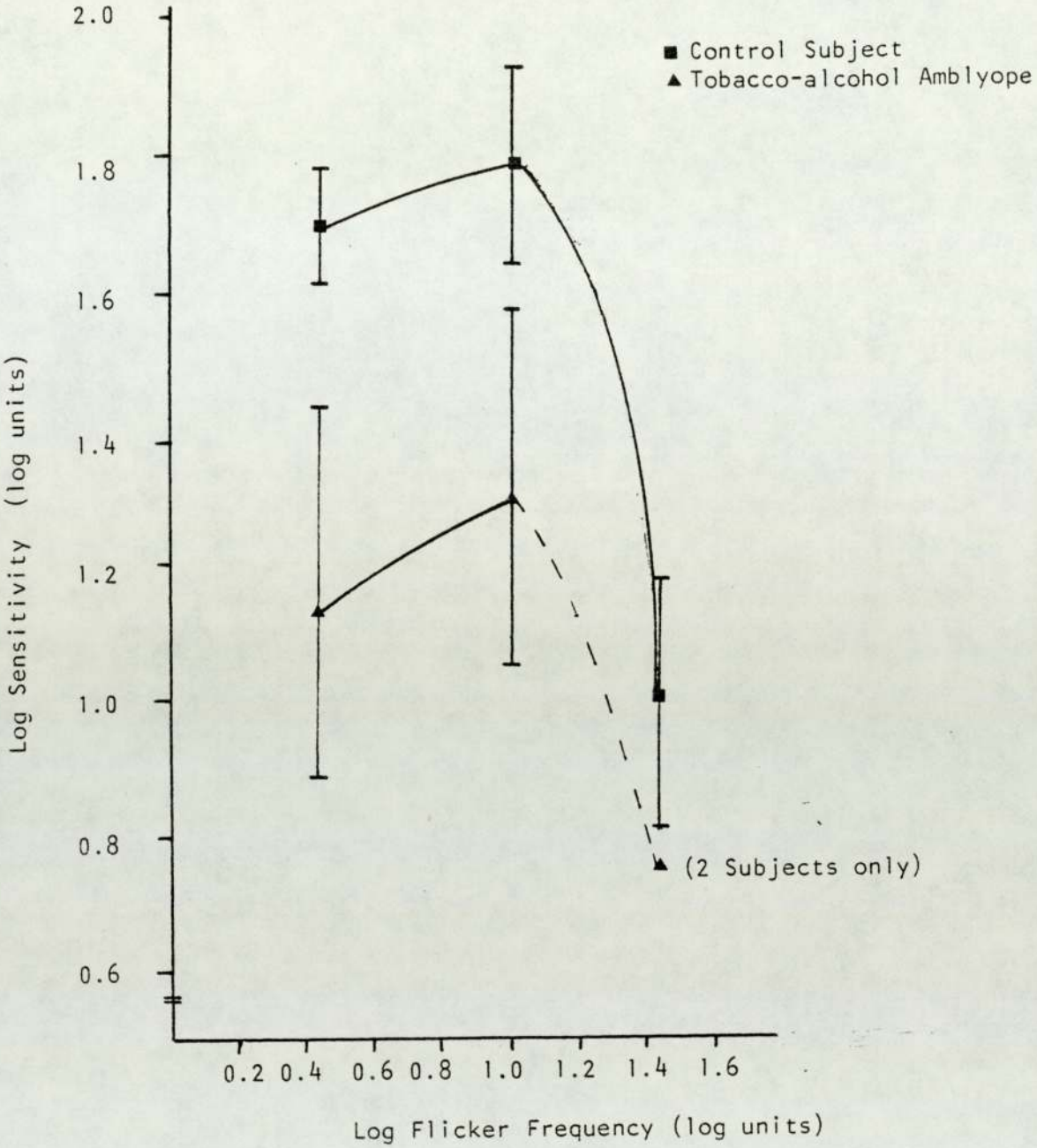


Figure 5.21.

Graph showing the means ±1SD for log sensitivity of the flicker fusion thresholds in 7 tobacco-alcohol amblyopes and 7 control subjects.

Subject Group	LOG SENSITIVITY (log units)		
	3 Hz	10 Hz	30 Hz
	R L	R L	R L
1	1.1334±0.2730/1.150±0.2335	1.2903±0.259/1.2464±0.230	5 subjects did not perceive the flicker effect.
2	1.6693±0.0927/1.6427±0.0784	1.7601±0.1473/1.8014±0.1566	0.9682±0.1860/0.9865±0.2155
F Value for Eyes DF	0.07 1,6 NS	1.83×10^{-3} 1,6 NS	Not analysed.
F Value for Groups DF	25.21 1,6 p<0.01	16.02 1,6 p<0.01	
F Value for Interaction DF	1.61 1,6 NS	1.78 1,6 NS	

Table 5.56 Giving the means ± 1SD for the log sensitivity of the flicker fusion thresholds in 7 tobacco-alcohol amblyopes and 7 control subjects.

The number of subjects whose log sensitivities are reduced below normal limits for the age are shown in Table 5.57.

Flicker Frequency (Hz)	Right Eye	Left Eye
3	6	5
10	5	6
30	6	6

Table 5.57 Showing the number of tobacco-alcohol amblyopes whose log sensitivities of the flicker fusion thresholds fall below normal limits for the age.

On the repeat investigation of 3 subjects, it has been found that there is a noticeable improvement for the high flicker frequency 30 Hz) in 2 subjects (EH_1, CJ) with the third subject (NB) demonstrating normal values on both occasions. The CFF of the right eye of subject EH_1 increased so that both eyes instead of only the left eye (which also showed an improvement from 0.7107 to 0.8706) could be examined at 30 Hz. This subject also demonstrated abnormal results at 3 and 10 Hz which did not improve on the second investigation. The CFF values of subject CJ also increased from about 14 Hz in each eye to about 20 Hz. This subject also showed an improvement in log sensitivity at the other two frequencies in each eye (for the right eye at 3Hz, from 1.138 to 1.257; at 10 Hz, 1.2297 to 1.4240). Subject NB who had normal flicker fusion thresholds at 30 Hz but abnormal thresholds at 3 and 10 Hz, did not reveal any marked improvement on the repeat investigations.

5.3.3 General Discussion and Summary of Findings

The distance and near VAs of these patients varied from 3/60 to 6/9 and less than N_{48} to N_{10} respectively. On inspecting Table 5.46, it would appear that the ~~mean~~ near VAs are generally worse than the corresponding distance VAs, (in spite of the fact that the equivalent near acuity is worse than the distance VA in normal eyes). If a 56' check is considered, this should be equivalent to a VA of less than 6/60 and therefore it would be expected that only subject EH_2 should demonstrate abnormal VERs for 56' pattern stimulation. However, on looking at the results for pattern reversal 56' black/white stimulation, only one subject (EH_1) yields results within normal limits (Table 5.48). Although this abnormality in the results is not as obvious with onset-offset stimulation, still only 4 of the 7 subjects yield normal results. This could be partly due to the larger variability in the onset-offset data. Nevertheless, for both forms of pattern stimulation, there is further deterioration in the responses for coloured stimulation (Table 5.48, 5.51). Therefore, these results would suggest that whilst the Snellen acuity measurements are useful indicators of visual changes, they do not appear to detect early changes in the visual system. It is also indicated that near acuity measurements are better indicators than distance acuity measurements for this disease, however, more information can be extracted from the VER concerning the state of the visual pathways than from VA measurements, such as information about the conduction properties of the pathways to spatial and diffuse stimulation.

In the 3 patients who have been repeated, one of them (NB) showed improvement in his distance and near VAs, however, this has not been reflected in his VER results.

In all of the repeated patients, there was some increase in sensitivity in the white macular thresholds and visual field scores, For the log sensitivities of the flicker fusion thresholds, there was also more marked recovery of the high frequencies than for the lower frequencies.

On considering the case histories of the tobacco-alcohol amblyopes, it is seen that they all have a history of smoking tobacco and drinking alcohol, with one of the patients (JM) recorded as having poor nutrition as well. It has already been mentioned that either tobacco on its own (Reed and Drance, 1972; Foulds et al, 1974; Samples and Younger, 1981; Harrington, 1981) or alcohol on its own (Reed and Drance, 1972; Samples and Younge, 1981; Harrington, 1982) or a combination of these substances (Victor and Dreyfus, 1965; Duke-Elder 1975; Samples and Younge, 1981; Dang, 1981), can give rise to this deterioration in vision and for this reason, most workers refer to this condition as tobacco-alcohol amblyopia. Some workers have claimed that the two conditions can be separately identified by their visual field changes in that tobacco amblyopia produces centrocaecal scotomata, whereas alcohol amblyopia produces central scotomata (Harrington, 1971, 1981; Reed and Drance, 1972). However, other investigators were unable to confirm this finding (Carroll, 1944; Victor and Dreyfus, 1965; Duke-Elder, 1975). More recently, Samples and Younge (1981) reported that whilst central or centrocaecal scotomata were seen in

association with patients who only smoked, central scotomata were seen more often in patients who consumed only alcohol. In this study, the patients demonstrated both central and centro-caecal scotomata. It is interesting to note that they were either pipe (the majority) or cigar smokers and had long smoking and drinking histories.

From the postmortem studies on tobacco-alcohol amblyopes, degeneration of the optic nerve fibres corresponding to the distribution of the papillomacular bundle was observed, although it was not restricted to this area (Victor et al. 1960; Victor, 1963; Victor and Dreyfus, 1965). The results obtained in this study on the chronic alcoholics and tobacco-alcohol amblyopes would support this finding. In the chronic alcoholics, the VERs of the macular region especially to red and green have demonstrated the most abnormal results. The macular thresholds, especially to red, have also produced markedly different results to those of the control subjects, as well as the lower flicker frequencies for a macular (2^{o}) stimulus. There are also changes in the ERGs, especially the OP, which would indicate that there is retinal as well as optic nerve involvement in this condition.

Unfortunately, only 3 subjects returned for repeat investigations, however, from their results, it would seem that the tests (that is, the VERs, the lower flicker frequencies) which have been found to be most sensitive in detecting early visual changes, are more resistant in recovering after damage has taken place. Nevertheless, there is an indication from the other tests that some recovery occurs although it may be a fairly slow process (2 of the repeated

patients were receiving cytamen injections, one of whom had already been getting them for 2 years). The pathogenesis of this condition still remains controversial for which many postulations have been made. However, it seems as if there are many influencing factors, such as cyanide from tobacco smoke, deficiencies in vitamins A_1, B_6 and B_{12}, folate, glutathione and sulphur-containing amino acids.

5.4 Data for Patients on Tuberculotic Therapy

The format of investigation for the patients on treatment for tuberculosis differs from that for the chronic alcoholics, in that the tuberculotic patients have been repeated twice after the initital investigation (before, during and after Ethambutol therapy). (Table 5.58). Hence, their results have been compared for the three visits using two-way ANOVA for related samples (Appendix 5, Table 19).

5.4.1 Electrophysiological Data

Electroretinograms

For the dark-adapted ERG, no significant difference has been obtained for the peak latencies or amplitudes of the components measured (Table 5.59). However, for the photopic ERG, a significant difference has been obtained for the B-wave latency ($p<0.05$) but no other marked changes have been seen.

Visual Evoked Responses

The results for flash stimulation reveal that a significant change ($p<0.01$) has occurred during the course of treatment with Ethambutol. From Table 5.60, it can be seen that there is a marked increase in the mean peak latency of the P_2 component for the second investigation, which is decreased for the third investigation but it is still delayed in comparision to its initial value (Table 5.60). Three (20%) of the 15 subjects demonstrated latencies which were

Subject Age (Yr) Sex Race	Visual Acuity RE/LE 1st Visit RE/LE 2nd Visit RE/LE 3rd Visit	Pupil Size (mm)	Ocular Changes	Dosage of drugs used for Tuberculotic Treatment	Other Medication	EMB Serum Level mg/l	Period Between Start of Treatment and 2nd Visit (Week)	Period Between Cessation of EMB and 3rd Visit (Week)	Renal Function	Tests Performed 1st Visit 2nd Visit 3rd Visit
NJ 16 F As (1T)	6/5-2N5 6/5-2N5 6/5-2N5 6/5N5 6/5-2N5 6/5N5	5.5A	NAD	15.5 mg/kg EMB 5.8 mg/kg INH 8.7 mg/kg RMP	Nil	-	6	4	NAD	ERG, VER ERG, VER, MT, VF ERG, VER, MT, VF
SQ 16 F As (2T)	6/5-1N5 6/5-1N5 6/5N5 6/5-1N5 6/5N5 6/5-1N5	5.5A	NAD	14.6 mg/kg EMB 7.3 mg/kg INH 11.0 mg/kg RMP	Nil	-	7	5	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
MH 19 M As (3T)	6/5N5 6/5N5 6/5N5 6/5N5 6/5N5 6/5N5	5.5A	NAD	13.2 mg/kg EMB 4.9 mg/kg INH 9.9 mg/kg RMP	Nil	4.7	11	7	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
HB 21 F As (4T)	6/9+2N5 6/9+2N5 6/9+3N5 6/9+2N5 6/9+2N5 6/9+2N5	4A	NAD	14.7 mg/kg EMB 6.3 mg/kg INH 12.6 mg/kg RMP	Ferrous Sulphate tablets. (anaemia)	-	7	10	NAD	ERG,VER ERG,VER ERG,VER
RB 24 F As (5T)	6/5-3N5 6/5-3N5 6/5-4N5 6/5-4N5 6/5-4N5 6/5-4N5	4A	NAD	15.4 mg/kg EMB 4.6 mg/kg INH 9.2 mg/kg RMP	Nil	7 decreased to 4.1 after 4 weeks.	12	7	Increased creatinine level	ERG,VER,FM ERG,VER,FM,MT ERG,VER,FM,MT
SL 26 F As (6T)	6/5N5 6/5N5 6/5-1N5 6/5N5 6/5N5 6/5-1N5	4.5A	NAD	15.6 mg/kg EMB 5.2 mg/kg INH 10.4 mg/kg RMP	Nil	2.4	19	7	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
BL 28 F As (7T)	6/5-3N5 6/6+3N5 6/5-2N5 6/6+4N5 6/5-3N5 6/6+3N5	4.5A	NAD	16.6 mg/kg EMB 6.2 mg/kg INH 9.4 mg/kg RMP	Nil	-	7	7	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
SK 31 F As (8T)	6/6N5 6/6N5 6/6-1N5 6/6N5 6/6-1N5 6/6N5	5A	NAD	20.4 mg/kg EMB 5.1 mg/kg INH 7.6 mg/kg RMP	Nil	3.4	6	8	NAD	ERG,VER,FM ERG,VER,FM,MT ERG,VER,FM,MT
PK 32 M WI (9T)	6/5N5 6/5N5 6/5N5 6/5N5 6/5N5 6/5N5	4.5A	NAD	14.0 mg/kg EMB 3.5 mg/kg INH 7.0 mg/kg RMP	Nil	4.7	8	8	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
MK 35 M As (10T)	6/5-1N5 6/5-1N5 6/5N5 6/5-1N5 6/5N5 6/5-1N5	5.5A	NAD	16.9 mg/kg EMB 4.2 mg/kg INH 8.4 mg/kg RMP	Nil	1.4	6	4	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
RL 36 M Cau (11T)	6/5N5 6/5N5 6/5N5 6/5N5 6/5N5 6/5N5	4A	NAD	16.3 mg/kg EMB 4.9 mg/kg INH 9.8 mg/kg RMP	Nil	2.7	8	7	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF
BS 41 F As (12T)	6/6+3N5 6/6-1N5 6/6+2N5 6/6-1N5 6/6+2N5 6/6N5	4A	NAD	14.3 mg/kg EMB 5.4 mg/kg INH 8.1 mg/kg RMP	Nil	4.6	7	10	NAD	ERG,VER,FM ERG,VER,FM,MT ERG,VER,FM,MT
AM 43 M As (13T)	6/5-2N5 6/5-2N5 6/5-3N5 6/5-1N5 6/5-3N5 6/5-1N5	4A	NAD	14.7 mg/kg EMB 3.7 mg/kg INH 7.3 mg/kg RMP	Nil	-	6	6	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MR,VF
MB 53 F As (14T)	6/6-1N5 6/9+2N6 6/6-1N5 6/9+2N6 6/6-1N5 6/9+2N6	3.5A	Seen on 1st visit. Fine pigmentation around each macula glial striae from each optic disc.	13.0 mg/kg EMB 4.4 mg/kg INH 8.7 mg/kg RMP	Aldomet (Hypertension)	-	8	7	Increased urea level.	ERG,VER ERG,VER ERG,VER
MI 58 F Cau (15T)	6/5-2N5 6/5-2N5 6/5-3N5 6/5-3N5 6/5-2N5 6/5-3N5	3.5A	NAD	15.0 mg/kg EMB 6.4 mg/mg INH 9.6 mg/kg RMP	Nil	2.2	8	10	NAD	ERG,VER,FM ERG,VER,FM,MT,VF ERG,VER,FM,MT,VF

Key: As - Asian, WI - West Indian, Cau - Caucasian
A - Active S - Sluggish
EMB - Ethambutol INH - Isoniazid RMP - Rifampicin
ERG - Electroretinogram VER - Visual Evoked Response FM - Flicker Fusion Threshold
MT - Macular Threshold VF - Visual Field.

TABLE 5.58 Giving the particulars of the visually symptomless tuberculotic patients

	Dark-Adapted Low Intensity			Photopic				
No. of Visit.	A (ms) R L	B (ms) R L	AB (uV) R L	A (ms) R L	B (ms) R L	OP1 (ms) R L	OP2 (ms) R L	AB (uV) R L
Visit 1	24.48±1.65/ 24.46±1.87	47.31±2.72/ 47.35±2.93	245.19±47.00/ 239.82±36.24	19.00±0.97/ 19.17±1.10	39.96±2.77/ 40.16±2.96	23.57±1.51/ 23.62±1.33	30.15±1.59/ 30.26±1.35	97.07±33.37 104.70±36.71
Visit 2	24.66±1.90 24.93±1.79	47.16±3.11/ 48.11±3.09	238.26±40.79/ 251.94±34.55	19.35±1.39 19.09±1.29	40.85±2.61/ 40.93±2.60	23.67±1.45/ 23.74±1.50	30.42±1.56/ 30.19±1.57	106.22±34.22 103.77±34.61
Visit 3	24.76±1.87/ 24.69±1.45	47.91±2.92/ 47.67±2.58	239.57±34.89/ 233.32±36.91	19.07±0.82/ 19.49±1.00	40.69±2.24/ 41.05±2.40	24.07±1.51/ 24.07±1.11	30.45±1.30/ 30.50±1.11	96.83±31.85, 97.60±29.53
F Value for eyes DF	0.05 1,13 NS	0.49 1,13 NS	0.03 1,13 NS	1.58 1,14 NS	3.68 1,14 NS	0.13 1,14 NS	0.76 1,14 NS	0.61 1,14 NS
F Value for visits DF	0.39 2,26 NS	0.47 2,26 NS	0.84 2,26 NS	1.28 2,28 NS	3.75 2,28 $p<0.05$	2.08 2,28 NS	0.59 2,28 NS	0.56 2,28 NS
F Value for inter-action DF	0.42 2,26 NS	3.33 2,26 NS	3.17 2,26 NS	2.91 2,28 NS	0.82 2,28 NS	0.04 2,28 NS	1.24 2,28 NS	3.32 2,28 NS

TABLE 5.59 Giving means ± 1 SD for the components of the dark-adapted and photopic ERGs in 15 (14 for the dark adapted ERG) visually unaffected tuberculotic patients on three investigations.

No. of Visit	P_2 (ms) R	P_2 (ms) L	N_2P_2 (uV) R	N_2P_2 (uV) L
Visit 1	128.57±5.71	128.78±6.50	7.24±3.52	7.37±3.56
Visit 2	135.12±11.85	133.88±8.97	5.39±2.15	5.55±2.33
Visit 3	132.71±8.32	132.37±7.81	5.69±2.24	5.78±2.56
F Value for Eyes DF	0.29 1,14	NS	0.24 1,14	NS
F Value for Visits DF	5.57 2,28	$p<0.01$	5.51 2,28	$p<0.01$
F Value for Interaction DF	0.32 2,28	NS	0.01 2,28	NS

TABLE 5.60 Giving means ± 1SD for the P_2 component and N_2P_2 configuration for flash stimulation in 15 visually unaffected tuberculotic patients on three investigations.

beyond normal limits (using mean plus two standard deviations as the criterion) for the age. The amplitudes of the N_2P_2 configuration also reveal a significant change with a reduction in amplitude for the second investigation and some increase in amplitude for the third investigation ($p<0.01$) (Table 5.60). One subject (6T) who was repeated for a third time, that is three months after all medication was stopped, showed P_2 latencies which had returned to their original values and a marked improvement in the amplitude of the N_2P_2 configuration (Figure 5.22)

On inspecting the results for pattern reversal stimulation (Table 5.61-5.63). there are no significant differences for the mean P_2 latency values for the larger check size (56') to black/white and coloured stimulation. For the smaller check size (14'), significant values have been attained for black/white and red/green stimulation ($p<0.05$). The responses of 2 subjects (6T, 15T) demonstrated marked changes although the latencies of the P_2 component did not fall outside normal limits (Figure 5.23). The morphology of the responses of another subject (12T) deteriorated to such an extent on the second investigation that they could not be included in the statistical analysis (Figure 5.24). This change in morphology was not seen in any other subject. Like the mean flash P_2 latencies, an increase in latency is seen for the second investigation with some decrease in latency for the third investigation.

No marked changes are observed for the amplitudes of the N_2P_2 configuration for any form of pattern reversal stimulation.

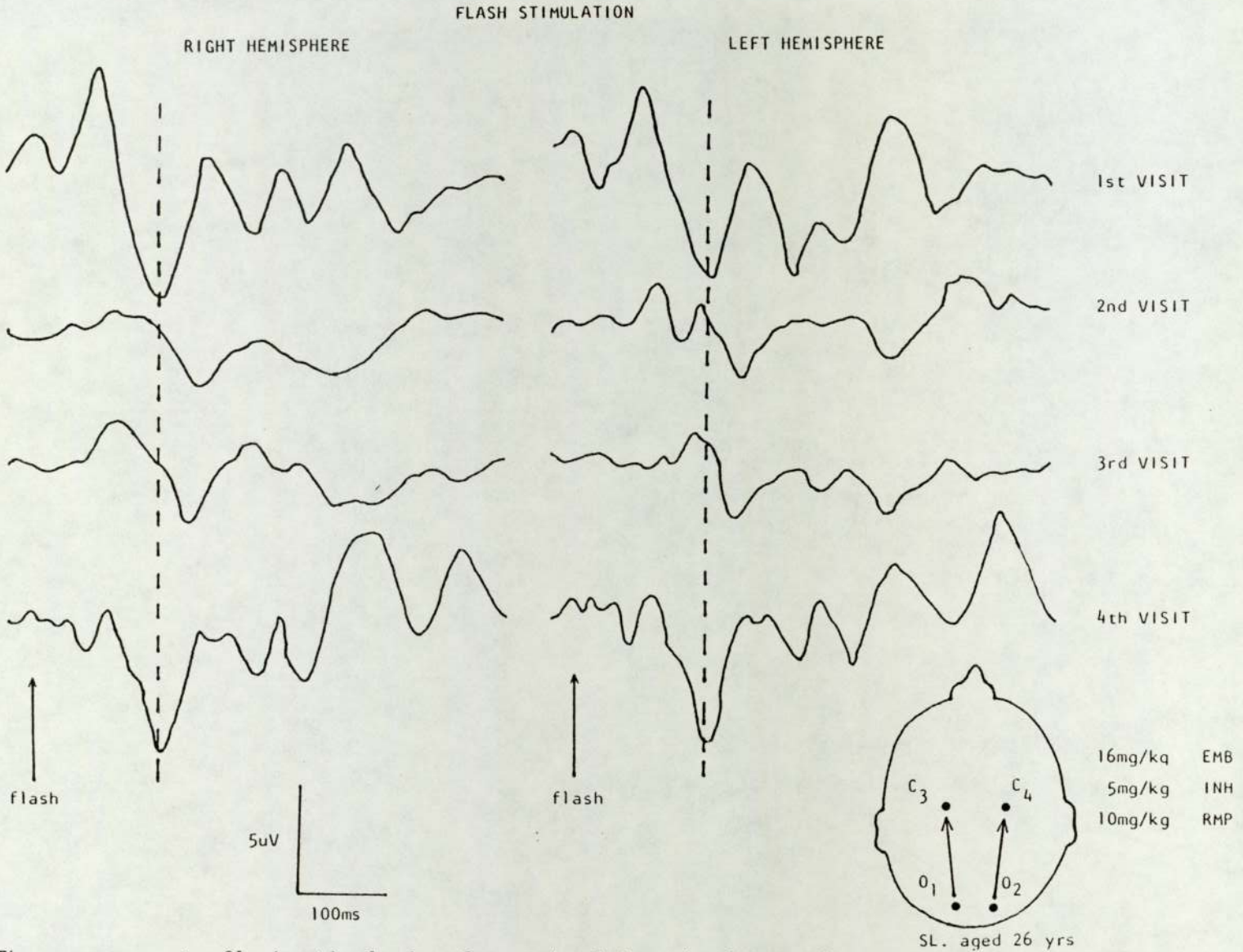


Figure 5.22 The responses to flash stimulation for each visit, showing an increase in latency of the P2 component and a reduction in amplitude of the N2-P2 configuration whilst on therapy. On the third visit after cessation of Ethambutol, there is some improvement although the VER has not returned to its original state. Patient and treatment details are shown. On the fourth visit after the cessation of all medication for 3 months, the VER returned to its original state.

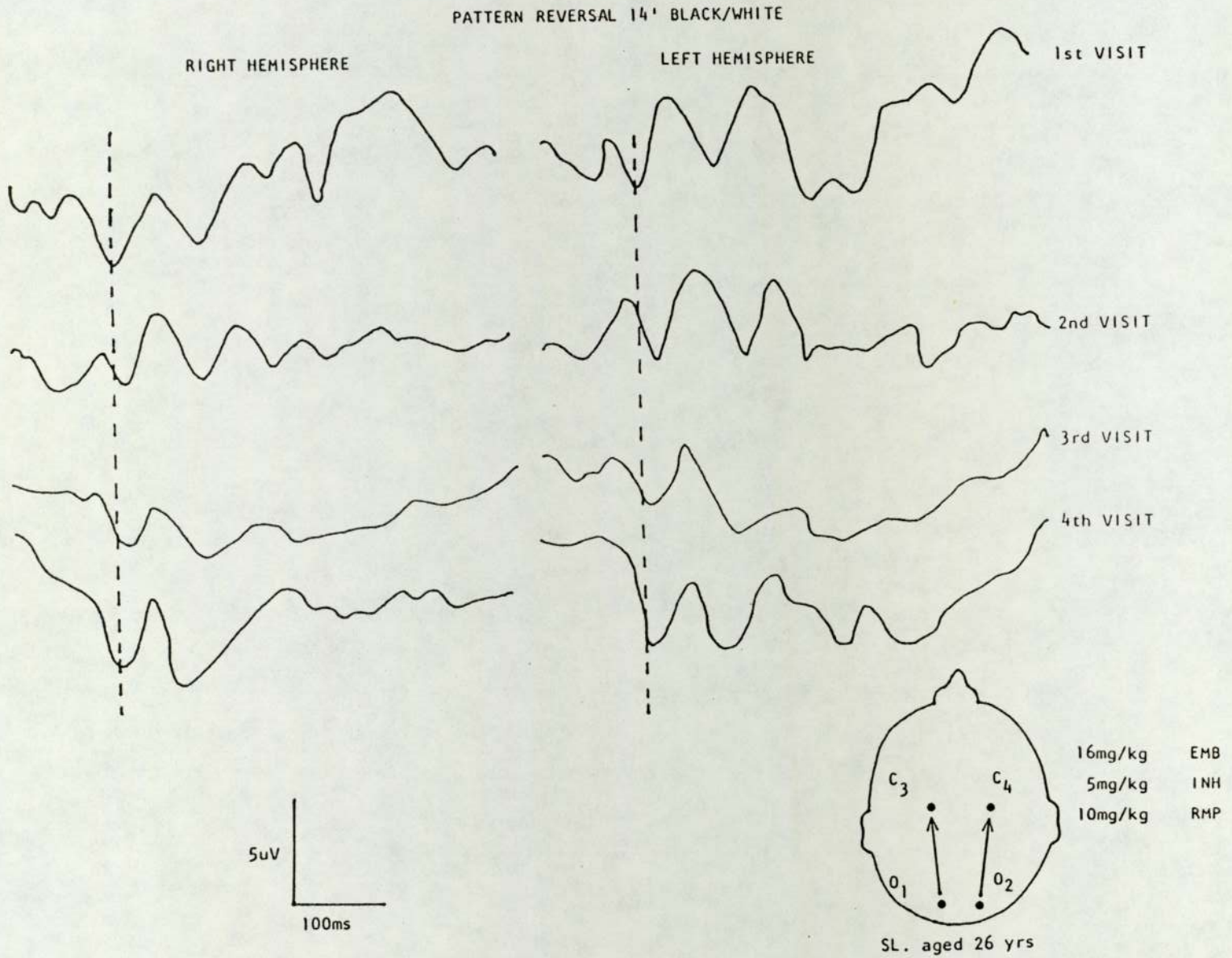


Figure 5.23 Responses to pattern reversal stimulation using a small check size, demonstrating an increase in latency of the component on the second (during treatment) and third (post Ethambutol) visits. Although the component was delayed, it never exceeded normal limits for the age. On the fourth visit, there was a reduction in the latency of the P2 component.

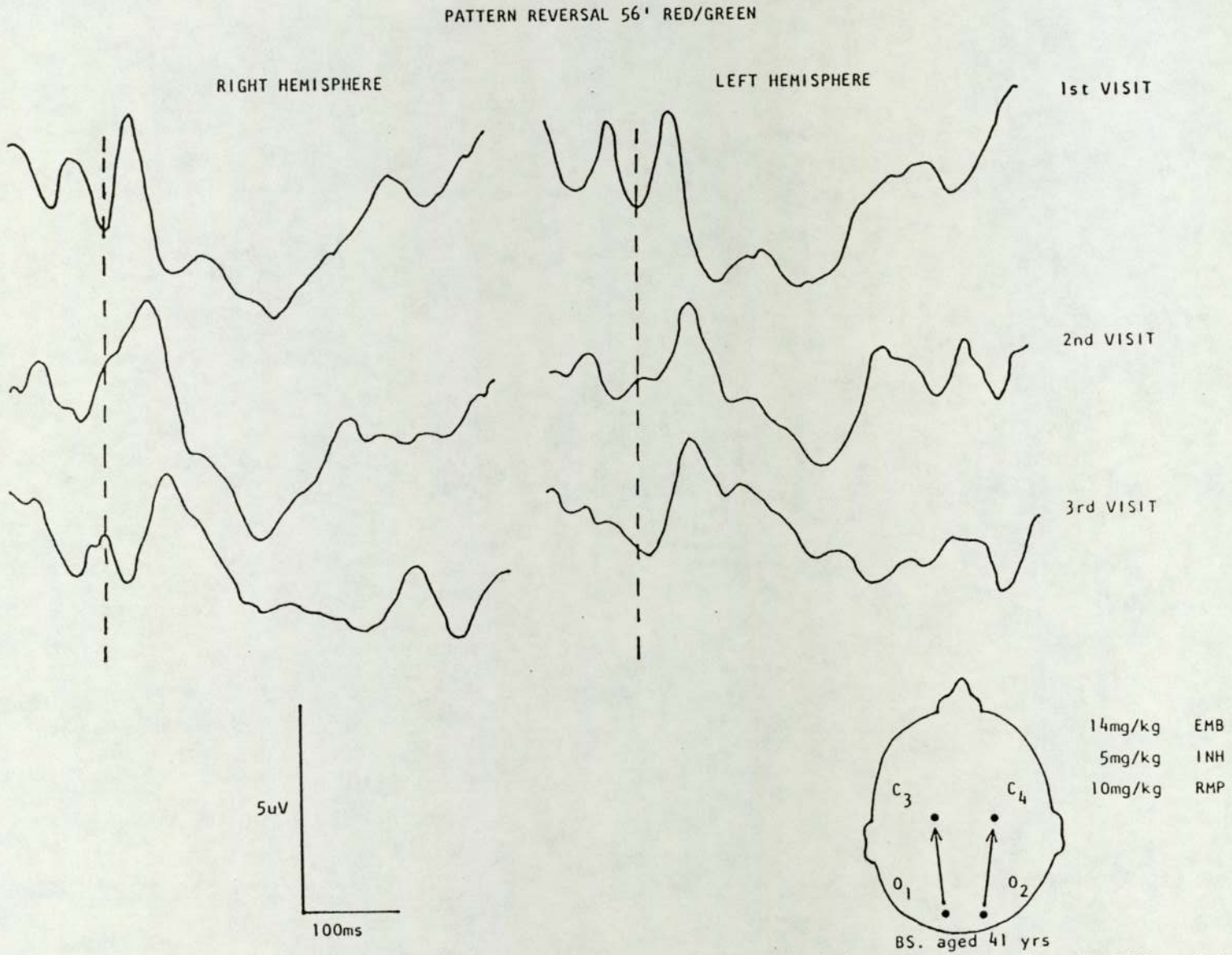


Figure 5.24 Pattern reversal responses of a patient who demonstrated a marked deterioration in the VERs with a reduction in amplitude of the N2-P2 configuration and a general change in the morphology during treatment. Similar changes were seen in all responses to a variety of pattern reversal checkerboards and also to flash. Following Ethambutol withdrawal there is some improvement in the P2 component.

No. of Visit	P_2 (ms) R	L	N_2P_2 (uV) R	L	P_2 (ms) R	L	N_2P_2 (uV) R	L
Visit 1	101.55±5.68/101.72±5.32		5.90±3.12/5.55±2.03		103.48±6.34/104.43±5.89		2.97±0.86/3.26±1.37	
Visit 2	103.10±5.53/102.67±4.45		5.77±2.40/5.51±2.44		107.09±8.05/108.64±7.77		3.42±1.60/3.31±1.17	
Visit 3	102.57±4.59/102.30±4.44		4.64±2.27/4.69±1.43		105.73±5.51/106.00±5.91		3.07±0.72/3.04±0.82	
F Value for Eyes	0.44		1.11		1.94		0.20	
DF	1,14	NS	1,14	NS	1,13	NS	1,13	NS
F Value for Groups	2.79		2.36		5.27		0.56	
DF	2,28	NS	2,28	NS	2,26	$p<0.05$	2,26	NS
F Value for Interaction	0.53		0.61		0.30		1.25	
DF	2,28	NS	2,28	NS	2,26	NS	2,26	NS

TABLE 5.61 Giving the means ±1 SD for the P_2 component and N_2P_2 configuration for pattern reversal black/white stimulation (56' and 14') in 15 visually unaffected tuberculotic patients on three investigations.

No. of Visit	P_2 (ms) R	L	N_2P_2 (uV) R	L	P_2 (ms) R	L	N_2P_2 (uV) R	L
Visit 1	108.88±6.34/109.00±5.69		4.24±2.49/4.40±2.65		105.05±7.86/106.57±7.39		3.03±1.08/2.76±0.87	
Visit 2	111.88±7.70/111.50±6.59		3.56±1.27/3.67±1.24		110.29±12.02/111.86±11.49		3.03±1.07/3.24±1.08	
Visit 3	109.77±7.19/110.17±6.76		3.49±1.16/3.47±1.19		108.68±10.53/108.98±10.16		2.95±0.93/2.87±0.71	
F Value for eyes	6.60×10^{-3}		0.97		3.82		0.62	
DF	1,14	NS	1,14	NS	1,13	NS	1,13	NS
F Value for groups	3.33		2.26		3.66		1.27	
DF	2,28	NS	2,28	NS	2,26	$P < 0.05$	2,26	NS
F Value for Interaction	0.26		0.18		1.00		0.59	
DF	2,28	NS	2,28	NS	2,26	NS	2,20	NS

TABLE 5.62 Giving the means ± 1 SD for the P_2 component and N_2P_2 configuration for pattern reversal red/green stimulation (56' and 14') in 15 visually unaffected tuberculotic patients on three investigations.

No. of Visit	P_2 (ms) R	L	N_2P_2 (uV) R	L	CII (ms) R	L	CI CII (uV) R	L
Visit 1	106.22±7.02/106.27±7.15		3.15±1.93/3.69±1.80		145.21±8.75/146.19±8.18		6.87±2.96/6.31±2.77	
Visit 2	107.80±7.87/108.07±8.38		3.51±1.69/3.50±1.39		149.21±8.09/149.50±7.76		5.71±3.70/6.24±2.93	
Visit 3	106.82±7.49/106.50±8.32		3.24±1.20/3.18±0.95		148.10±9.72/148.83±7.80		5.04±2.70/5.02±2.40	
F Value for Eyes	0		0.08		0.82		2.14×10^{-3}	
DF	1,14	NS	1,14	NS	1,14	NS	1,14	NS
F Value for Visits	2.20		0.50		5.19		1.73	
DF	2,28	NS	2,28	NS	2,28	$p<0.05$	2,28	NS
F Value for Interaction	0.17		0.39		0.14		1.31	
DF	2,28	NS	2,28	NS	2,28	NS	2,28	NS

TABLE 5.63 Giving means ± 1 SD for the P_2 and CII components and N_2P_2 and CI CII configurations for pattern reversal and pattern onset-offset blue/yellow (56^t) stimulation respectively in 15 visually unaffected tuberculotic patients on three investigations.

Unlike the P_2 latencies for pattern reversal 56' stimulation, the mean CII latencies for 56' pattern onset-offset stimulation have shown marked differences for black/white, blue/yellow and red/green stimulation ($p<0.05$;Table 5.63-5.65). The CII latencies for the smaller check size have also attained significance at the 5% level for black/white and red/green stimulation. The amplitude of the CI CII configuration have not revealed any marked differences over the three investigations.

5.4.2 Psychophysical Results

Visual Fields

Unfortunately, due to circumstances beyond the experimenter's control, it was not possible to examine the visual fields of the patients on the first occasion and therefore, results are only shown for the second and third investigations. This could have contributed to the finding that no significant results have been obtained for either the macular thresholds or visual scores on the 12 and 10 patients examined respectively (Table 5.66). However, in the patients that were tested, all of the values were within normal limits.

The Fusion Thresholds to Flicker Stimulation at 3, 10 and 30 Hz

The log sensitivities to flicker fusion have not demonstrated any marked differences for any of the flicker frequencies used (Table 5.67).

No. of Visit	CII(ms) R	CII(ms) L	CI CII (uV) R	CI CII (uV) L	CII (ms) R	CII (ms) L	CI CII (uV) R	CI CII (uV) L
Visit 1	106.12±15.15/106.62±13.65		5.89±4.87/6.29±5.00		117.92±12.88/115.95±12.90		4.90±2.81/5.23±3.14	
Visit 2	109.22±14.46/110.50±15.26		5.20±2.72/5.14±2.47		122.58±16.08/122.38±15.64		4.92±3.05/4.68±2.96	
Visit 3	110.85±15.56/110.50±14.22		5.48±3.16/5.10±3.21		122.18±14.47/122.27±13.89		4.72±2.04/4.88±2.52	
F Value for Eyes	1.16		1.72×10^{-3}		2.15		0.23	
DF	1,14	NS	1,14	NS	1,14	NS	1,14	NS
F Value for Visits	5.36		0.69		6.69		0.11	
DF	2,28	$p < 0.05$	2,28	NS	2,28	$p < 0.05$	2,28	NS
F Value for Interaction	1.07		0.74		1.94		1.57	
DF	2,28	NS	2,28	NS	2,28	NS	2,28	NS

TABLE 5.64 Giving means ± 1SD for the CII component and CI CII configuration for pattern onset-offset black/white stimulation (56' and 14') in 15 visually unaffected tuberculotic patients on three investigations.

Nos. of Visits.	CII(ms) R	CII(ms) L	CI CII (uV) R	CI CII (uV) L	CII(ms) R	CII(ms) L	CI CII (uV) R	CI CII (uV) L
Visit 1	123.97±12.88/125.52±13.84		6.49±3.96/6.54±3.99		132.96±14.22/134.68±12.73		6.52±2.76/6.16±3.30	
Visit 2	129.08±12.14/129.45±12.33		6.49±3.96/6.32±3.54		139.30±12.79/137.71±13.51		6.64±2.80/6.24±3.11	
Visit 3	127.18±12.55/128.38±13.02		5.43±2.05/5.15±2.68		138.30±11.86/136.79±13.08		5.34±1.95/5.30±2.50	
F Values for eyes	2.98		0.44		0.48		1.02	
DF	1,14	NS	1,14	NS	1,13	NS	1,14	NS
F Values for visits	6.41		1.38		6.38		1.90	
DF	2,28	$p < 0.05$	2,28	NS	2,26	$p < 0.05$	2,28	NS
F Value for Interaction	2.21		0.26		2.52		0.33	
DF	2,28	NS	2,28	NS	2,26	NS	2,28	NS

TABLE 5.65 Giving means ± 1 SD for the CII component and CI CII configuration for pattern onset-offset red/green stimulation (56' and 14') in 15 visually unaffected tuberculotic patients on three investigations.

No. of Visit	MACULAR THRESHOLD (log units)								Visual Field Score (log units).	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L	R	L
Visit 2	2.58±0.24/2.58±0.24 (2.0-2.8)	(2.0-2.8)	2.40±0.18/2.40±0.15 (2.2-2.6)	(2.2-2.6)	1.89±0.21/1.85±0.22 (1.6-2.2)	(1.4-2.2)	0.89±0.14/0.91±0.16 (0.6-1.0)	(0.6-1.2)	225.86±10.99/227.32±11.28	
Visit 3	2.62±0.21/2.62±0.21 (2.2-2.8)	(2.2-2.8)	2.42±0.17/2.40±0.18 (2.2-2.6)	(2.2-2.6)	1.91±0.26/1.91±0.19 (1.4-2.2)	(1.6-2.2)	0.95±0.16/0.95±0.16 (0.6-1.2)	(0.6-1.2)	226.6±10.56/228.97±9.23	
Non zero value (n)	2	3	1	2	4	3	6	7	9	10
T value for R & L eyes Between Visits.	0	0	0	1	4	0	6	12.5	13	26
	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	NS	NS	NS	NS
Non zero value (n)	1		2		4		1		1	
T value for interocular difference for visit 2	0		1		2.5		0		6	
	Unspecified		Unspecified		Unspecified		Unspecified		NS	

TABLE 5.66 Giving (means ± 1 SD) and ranges for the macular thresholds and visual field scores in 12 (10 for the visual field scores) visually unaffected tuberculotic patients on two investigations.

LOG SENSITIVITY (log units)

No. of Visit	3 Hz R	3 Hz L	10 Hz R	10 Hz L	30 Hz R	30 Hz L
Visit 1	1.6894±0.0985/1.6923±0.0964		1.8255±0.1093/1.8094±0.0954		1.1464±0.2256/1.1379±0.2172	
Visit 2	1.7027±0.0864/1.7372±0.0840		1.8512±0.1122/1.8413±0.1068		1.1338±0.2088/1.1300±0.2025	
Visit 3	1.7012±0.0806/1.7203±0.0922		1.8381±0.1210/1.8353±0.0963		1.1088±0.2089/1.1245±0.2040	
F Value for eyes	3.41		1.27		0.01	
DF	1,10	NS	1,10	NS	1,10	NS
F value for visits	1.02		1.30		1.28	
DF	2,20	NS	2,20	NS	2,20	NS
F value for Interaction	1.26		0.27		1.06	
DF	2,20	NS	2,20	NS	2,20	NS

TABLE 5.67 Giving means ± 1 SD for the log sensitivities of the flicker fusion thresholds in 11 visually unaffected tuberculotic patients on three investigations.

5.4.3 General Discussion and Summary of Findings

The results which have been obtained for the photopic ERG, the flash and pattern VERs indicate that subclinical visual changes occur during the course of tuberculotic treatment with Ethambutol, Isoniazid and Rifampicin. Ethambutol, and to a lesser extent, Isoniazid have been reported as producing visual symptoms in patients on various dose levels, often above the recommended level. However, the dosages which were prescribed for the patients examined in this study are well within the recommended dose regime, with mean dose levels of 15.25 $\pm$ 1.87 mg/kg for Ethambutol, 5.18 $\pm$ 1.07 mg/kg for Isoniazid and 9.21 $\pm$ 1.57 mg/kg for Rifampicin.

Flash VER stimulation yielded the most significant results with both latency and amplitude changes taking place. Three of the 15 subjects also produced VERs which were not within normal limits. For both the more significant flash responses and the less significant pattern responses, a certain trend is observed in the results, in that there is an increase in latency on the second occasion and although some improvement is seen on the third occasion , the latencies have not returned to their previous values. The only subject who was repeated after complete cessation of treatment demonstrated a return to the original latency values. The above findings would suggest that Ethambutol has an effect upon the visual system during the course of treatment, however, after its cessation, either there is not full recovery from its effect or there is also some additional influence from Isoniazid which continues to take effect. From the ERG and VER results, it is indicated that these changes occur at both the retinal

and post-retinal levels, being more marked for the latter. From the ERG results, it is suggested that the photopic system is more affected than the scotopic system which is supported by the findings of Babel et al. (1977). However, Hennekes (1982) reported that the scotopic B wave is more affected than the photopic B wave in severe cases of Ethambutol toxicity studied by him. Perhaps, this discrepancy in the results could be due to the different methods used to assess the ERG data and the different stages at which the patients were examined.

The subclinical changes observed in the flash and pattern VERs in this study, occurred in patients who had VAs of at least 6/6-1 in each eye. In clinically affected patients with low VAs, Zrenner and Kruger (1981) reported delayed flash and pattern VERs due to Ethambutol toxicity. With the exception of one patient (11T), all of the other patients were teetotallers and non-smokers.

5.5 Data for Visually Affected Tuberculotic Patients Due to Ethambutol Toxicity

Six visually affected tuberculotic patients (4 males, 2 females, $\bar{x}$ = 51.5 ± 10.8 yr) diagnosed as suffering from Ethambutol toxicity have been examined and their results have been compared to those of 6 age-and-sex matched controls (Table 5.68). Two of these subjects (HS, EH) have been repeated after 19 and 4 months respectively.

5.5.1 Electrophysiological Results

Electroretinograms

The dark-adapted ERG is within normal limits in all of the subjects examined, however, the photopic ERG is poorly formed in 2 subjects (HS, MT) with only what appears to be an A wave present. (Table 5.69).

On the repeat investigation the photopic ERG of subject (HS) improved in form with the appearance of the OPs and the B wave (Figure 5.25).

Visual Evoked Responses

The data for the latencies have been analysed by the Fisher-Yates test of significance and that for the amplitudes by two-way ANOVA.

For flash stimulation, 4 of the 6 patients demonstrated abnormal responses and the results attained statistical significance ($p<0.03$).

Subject Age (yr) Sex Race	Visual Acuity RE/LE 1st Visit RE/LE 2nd Visit	Pupil Size (mm)	Ocular Changes	Dosage of drugs used for TB therapy (mg/kg)	Other Illnesses	Admin period of EMB/INH and Onset of Symptoms prior to 1st visit.	Period Between Cessation of EMB & INH & 1st Visit.	Period Between 1st & 2nd Visits
HS 40 M A	6/18+3N14 6/18 N18 6/9 N8 6/9-1 N8	5 4.5	NAD	Dosage of TB drugs - not known.	-	Not Known. --- 6/12	N/K	19/12
DS 42 M C	6/5 N5 6/12+2 N8	5	Mild diabetic retino-pathy	Dosage of TB drugs - not known.	Diabetes (tablets only)	EMB - 2/12 INH - 8/12 --- 4/12	EMB - 6/12 Still on INH & RMP	FTR
CS 46 M A	6/6-4N6 6/6-3 N6	4.5	NAD	14.6 EMB 3.2 INH 9.7 RMP	-	EMB - 25 days INH - 18/52 --- 6/52	EMB - 14/52 Still on INH and RMP	FTR
HA 55 M A	6/18 N24 6/18 N24	4	NAD	Dosage of TB drugs - not known.	Diabetes	Not known. --- 5/12	EMB - 4/12	FTR
MT 58 F A	6/36 6/24	3.5	Mild vascular retino-pathy with some exudates & haemo-rhages; slight optic disc pallor	13.6 EMB) 4.6 INH) for 8/12 6.8 RMP) Stopped all medication for 2/12, then re-started for the past 2/12 with: 15 INH (2x wkly) 0.25 Strep (2 x wkly) 10 mg Pyrid (daily)	Hyper-tension; Renal function impaired	EMB - 8/12 INH - 10/12 --- 5/12	EMB - 4/12 Still on INH	FTR
EH 68 F C	6/36<N48 2/60<N48 6/18 N24 6/18 N36	4.5 4.5	NAD	13.1 EMB 3.9 INH 7.9 RMP	Hyper-tension; asthma	EMB - 7/12 INH - 7/12 --- 5/12	EMB - 4/12 INH - 4/12	4/12

Key: A - Asian
C - Caucasian

EMB - Ethambutol
INH - Isoniazid
RMP - Rifampicin
Strep - Streptomycin

N/K - Not Known
FTR - Failed to return.

Table 5.68 Giving the particulars of the visually affected tuberculotic patients due to Ethambutol therapy.

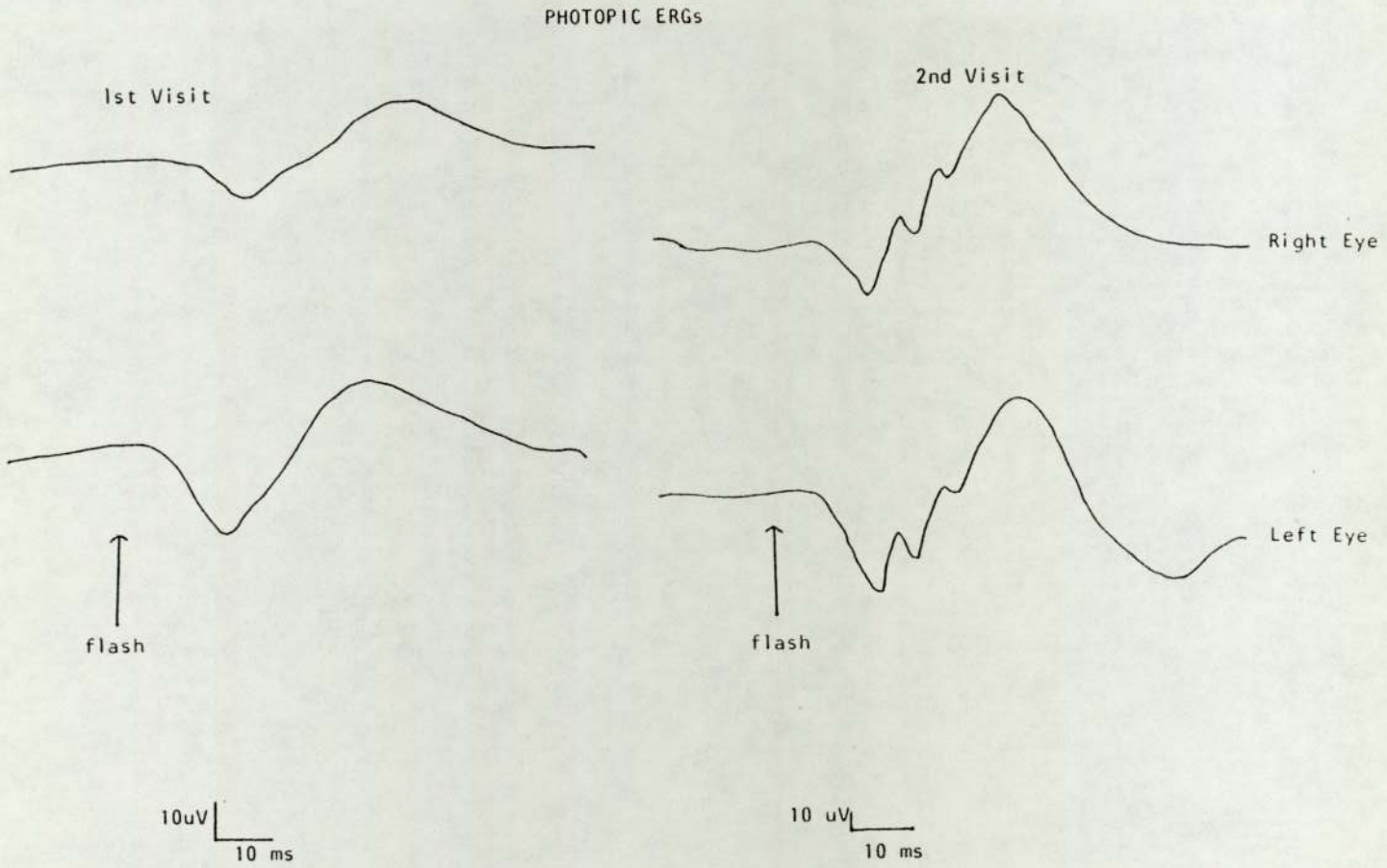


Figure 5.25 The photopic ERGs of a patient with Ethambutol toxicity whose responses showed an improvement in the appearance of the components and the amplitude of the AB configuration on the second investigation

	Dark-Adapted Low-Intensity					Photopic									
Subject Group	A(ms) R	A(ms) L	B(ms) R	B(ms) L	AB(uV) R	AB(uV) L	A(ms) R	A(ms) L	B(ms) R	B(ms) L	OP1(ms) R	OP1(ms) L	OP2(ms) R	OP2(ms) L	AB(uV) R	AB(uV) L
1	27.54±0.84/ 27.70±0.91		51.74±2.61/ 51.62±2.85		204.38±64.17/ 213.52±78.24		20.33±1.03/ 20.33±1.60		Indiscernible responses in two subjects						62.53±37.19/ 68.60±32.60	
2	26.00±2.02 26.04±2.04		50.38±2.07/ 50.40±2.53		230.86±36.97/ 232.00±28.09		21.25±0.52/ 21.33±0.98		43.75±0.52/ 43.50±2.52		23.65±1.64/ 24.50±1.34		31.50±0.71 32.00±0.71		73.37±16.47/ 75.35±17.61	
F Value for Eyes DF	0.19 1,4	NS	0.01 1,4	NS	1.50 1,5	NS	0.02 1,5	NS	Not analysed		Not analysed		Not analysed		1.22 1,5	NS
F Value for Groups DF	2.36 1,4	NS	0.44 1,4	NS	0.47 1,5	NS	4.05 1,5	NS							0.26 1,5	NS
F Value for Interaction DF	0.07 1,4	NS	0.02 1,4	NS	0.12 1,5	NS	0.06 1,5	NS							0.56 1,5	NS

Table 5.69 Giving means ± 1SD for the components of the dark-adapted and photopic ERGs in 6 tuberculotic patients and 6 control subjects.

Two of these subjects had indiscernible, low amplitude responses (MT, HA in the right eye only) with 2 subjects demonstrating PNP responses (HS, HA - in the left eye only). (Figure 5.26).

Pattern reversal 56' stimulation to black/white and blue/yellow have not revealed any significant results, however, the results for red/green are markedly different ($p<0.03$). Pattern reversal 14' 14' black/white and red/green stimulation have revealed more significant results ($p<0.008$) (Table 5.70). One subject (DS) demonstrated responses within normal limits for the various forms of stimulation (except 14' red/green stimulation) but there was a noticeable inter-ocular difference (Figure 5.27).

Similar to pattern reversal stimulation, pattern onset-offset 56' black/white stimulation has not produced significant results but for red/green and blue/yellow stimulation the probability level is 3%. For 14' black/white stimulation, the level of significance for the right eye is 3% whilst that for the left eye is 0.8%. This difference in the significance levels between the two eyes is due to the VERs of subject CS whose responses from the right are eye within normal limits and those from the left eye are abnormal. For 14' red/green stimulation, the level of significance is 0.8% (Table 5.71).

The amplitude of the N_2P_2 configuration to flash stimulation is observed to be significant ($p<0.01$). For pattern reversal 56' black/white and coloured stimulation, there is no marked difference, however, for the smaller check size, there is a marked difference for black/white ($p<0.01$) and red/green ($p<0.05$) stimulation. On the contrary, the

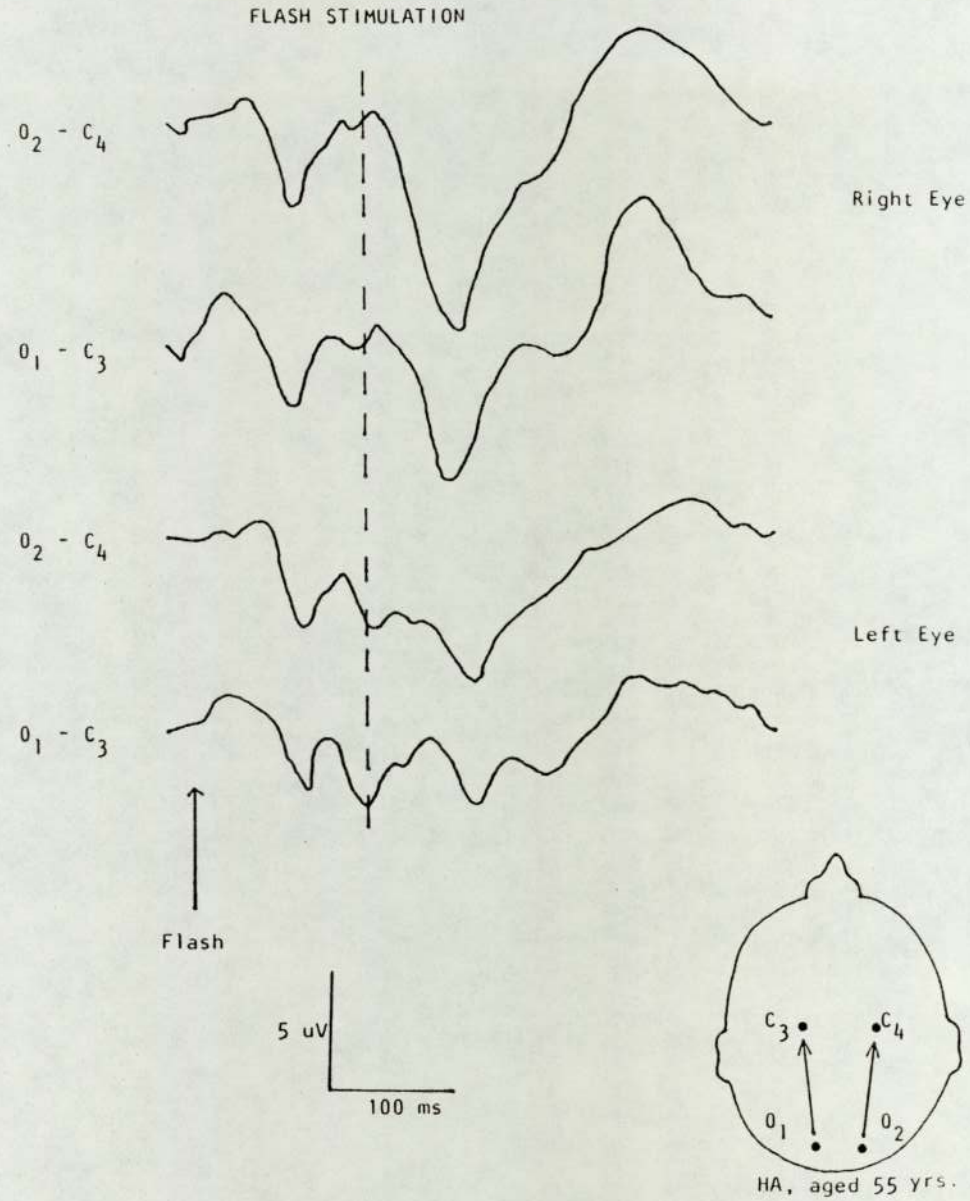


Figure 5.26 The VER to flash stimulation in a patient with Ethambutol toxicity, whose responses from the right eye were poorly formed and demonstrated a prominent P1 component but no P2 component whilst the responses from the left eye had a PNP waveform

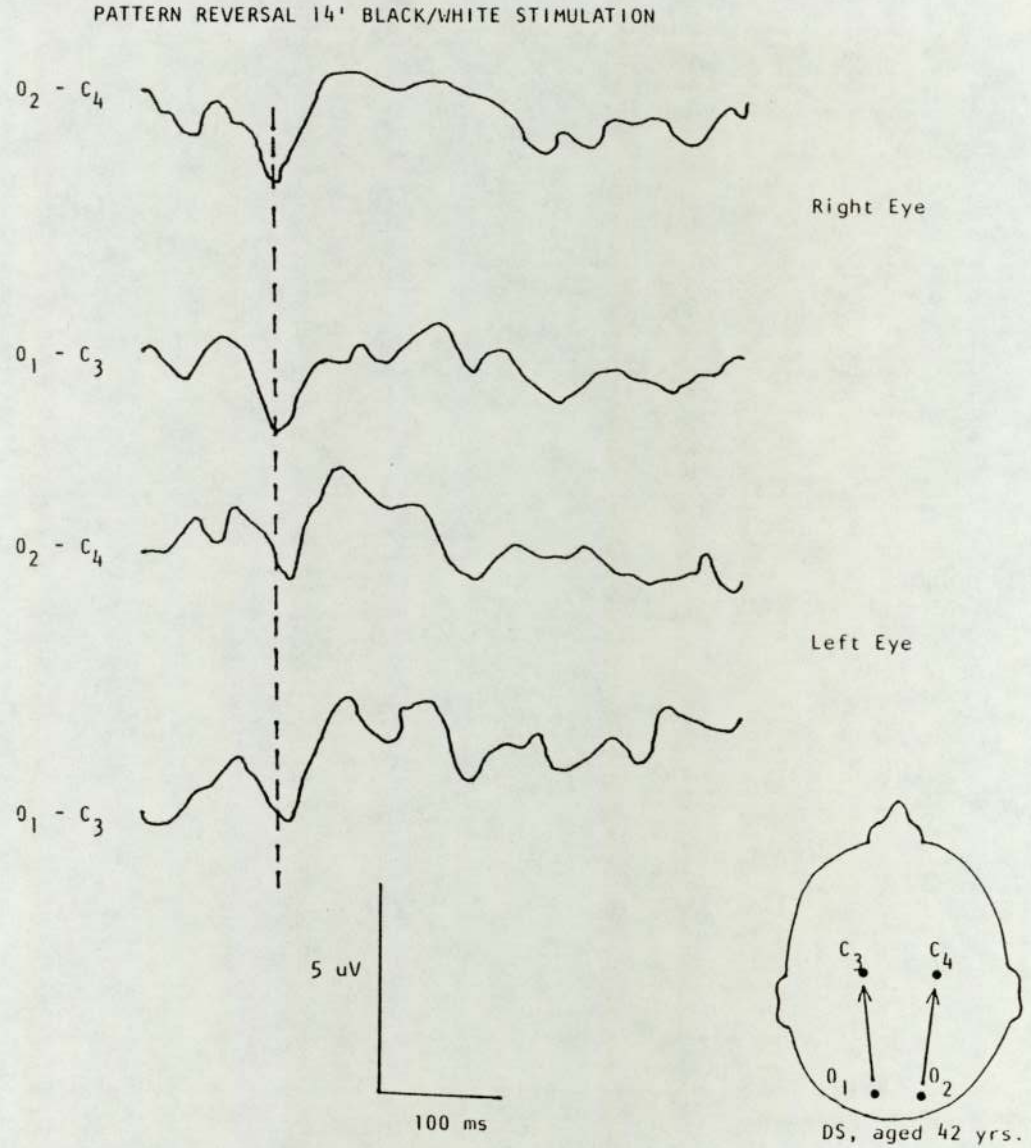


Figure 5.27 The VERs to pattern reversal 14' black/white stimulation in a patient with Ethambutol toxicity which demonstrated an interocular difference in latency of the P2 component.

Type of Stimulus	Right Eye	Control Subject	Tuber-culotic Patient	Signif-icance Level	Left Eye	Control Subject	Tuber-culotic Patient	Signif-icance Level
Flash	Normal Abnormal	6 0	2 4	$p<0.03$	Normal Abnormal	6 0	2 4	$p<0.03$
PR 56' B/W	Normal Abnormal	6 0	4 2	NS	Normal Abnormal	6 0	4 2	NS
PR 14' B/W	Normal Abnormal	6 0	1 5	$p<0.008$	Normal Abnormal	6 0	1 5	$P<0.008$
PR 56' R/G	Normal Abnormal	6 0	2 4	$p<0.03$	Normal Abnormal	6 0	2 4	$p<0.03$
PR 14' R/G	Normal Abnormal	6 0	1 5	$p<0.008$	Normal Abnormal	6 0	1 5	$p<0.008$
PR 56' B/Y	Normal Abnormal	6 0	3 3	NS	Normal Abnormal	6 0	3 3	NS

Key:- PR - Pattern reversal; B/W - Black/White; R/G - Red/Green; B/Y - Blue/Yellow.

TABLE 5,70 Showing the number of P_2 peak latencies which fall within or beyond normal limits for 6 control subjects and 6 visually affected tuberculotic patients.

Type of Stimulus	Right Eye	Control Subject	Tuber-culotic Patient	Signif-icance Level	Left Eye	Control Subject	Tuber-culotic Patient	Signif-icance Level
P O/N 56' B/W	Normal	6	4		Normal	6	4	
	Abnormal	0	2	NS	Abnormal	0	2	NS
P O/N 14' B/W	Normal	6	2		Normal	6	1	
	Abnormal	0	4	$p<0.03$	Abnormal	0	5	$p<0.008$
P O/N 56' R/G	Normal	6	2		Normal	6	2	
	Abnormal	0	4	$p<0.03$	Abnormal	0	4	$p<0.03$
P O/N 14' R/G	Normal	6	1		Normal	6	1	
	Abnormal	0	5	$p<0.008$	Abnormal	0	5	$p<0.008$
P O/N 56' B/Y	Normal	6	2		Normal	6	2	
	Abnormal	0	4	$p<0.03$	Abnormal	0	4	$p<0.03$

Key:- P O/N - Pattern onset/offset; B/W - Black/White; R/G - Red/Green; B/Y - Blue/Yellow.

TABLE 5.71 Showing the number of CII peak latencies which fall within or beyond normal limits for 6 control subjects and 6 visually affected tuberculotic patients.

significance levels are reversed for pattern onset-offset 14' black/white and red/green stimulation. This could be partly due to the tendency of the coloured responses to be lower in amplitude than those to black/white for pattern reversal, but not for pattern onset-offset. (Table 5.72-5.75).

On the repeated investigations for subjects (HS, EH) only minimal decreases in latency and amplitude are seen for flash stimulation. For subject HS on the first investigation, normal VERs are seen for pattern reversal and onset-offset 56' black/white and blue/yellow stimulation. However, for both forms of stimulation, a considerable interocular difference is observed for 56' red/green stimulation (11.25 ms for pattern reversal and 12.5 ms for the onset-offset. The VAs were similar in each eye). For pattern reversal 14' black/white stimulation, a VER is only seen in the left eye but there is no response for 14' red/green stimulation from either eye. The responses for 14' onset-offset stimulation are indiscernible. On the repeat investigation, theinterocular difference disappeared for pattern reversal and onset-offset 56' red/green stimulation but it is seen for pattern reversal and onset-offset 14' black/white stimulation. The VERs for red/green stimulation are still eliminated.

On the first investigation subject EH demonstrated delayed and low amplitude responses to a 2^{o} pattern reversal black/white stimulation, with only the right eye yielding a response (delayed) to 56', and indiscernible responses were obtained from either eye at 27'. Pattern onset-offset stimulation revealed normal responses to 2^{o} checks, a normal response (at the upper limits) from the right

Subject Group	PR 56' B/Y N_2P_2 (uV)	Flash N_2 P_2 (uV)
1	1.62±1.87/1.42±1.58	3.38±3.00/3.48±2.88
2	3.00±0.85/3.20±1.03	6.40±2.51/8.64±4.07
F Value for Eyes DF	7.95×10^{-4} 1,5 NS	1.82 1,5 NS
F Value for Groups DF	4.17 1,5 NS	35.11 1,5 p<0.01
F Value for Interaction DF	0.75 1,5 NS	0.79 1,5 NS

Table 5.72 Giving the means ± 1 SD for the amplitudes of the N_2P_2 configuration for flash and pattern reversal stimulation in 6 tuberculotic patients and 6 control subjects.

Subject Group	PR 56' B/W	PR 14' B/W	PR 56' R/G	PR 14' R/G
	N_2P_2 (uV)	N_2P_2 (uV)	N_2P_2 (uV)	N_2P_2 (uV)
1	4.60±2.47/3.62±2.87	1.24±1.93/1.55±1.72	1.79±2.01/1.67±1.82	1.05±1.64/1.07±1.73
2	5.06±1.27/4.33±1.48	4.29±1.52/5.33±2.19	3.76±1.09/3.65±1.25	3.98±0.89/4.21±1.41
F Value for Eyes DF	0.18 1,5 NS	5.27 1,5 NS	3.38 1,5 NS	0.32 1,5 NS
F Value for Groups DF	5.79 1,5 NS ~~p<0.05~~	19.83 1,5 p<0.01	4.44 1,5 NS	13.15 1,5 p<0.05
F Value for Interaction DF	0.17 1,5 NS	0.36 1,5 NS	2.53×10^{-5} 1,5 NS	0.13 1,5 NS

Key: 1 - Tuberculotic patients, 2 - Control subjects, PR - Pattern reversal, B/W - Black/White
R/G - Red/Green, B/Y - Blue/Yellow

Table 5.73 Giving the means ± 1 SD for the amplitude of the N_2P_2 configuration for pattern reversal stimulation in 6 tuberculotic patients and 6 control subjects.

Subject Grp	PO/N 56' B/W	PO/N 14' B/W	PO/N 56' R/G	PO/N 14' R/G
	CI CII (uV)	CI CII (uV)	CI CII (uV)	CI CII (uV)
1	6.44±5.40/6.37±5.79	3.93±2.88/3.43±1.86	5.24±4.42/5.12±4.10	3.13±3.64/3.10±4.27
2	5.43±3.75/5.60±2.39	5.95±1.07/5.69±0.95	8.10±4.94/7.08±2.65	8.10±5.09/7.86±2.05
F Value for Eyes	4.31×10^{-3}	0.75	0.54	0.12
DF	1,5 NS	1,5 NS	1,5 NS	1,5 NS
F Value for Groups	0.11	7.18	2.02	54.49
DF	1,5 NS	1,5 $p<0.05$	1,5 NS	1,5 $p<0.01$
F Value for Interaction	0.02	0.05	0.66	0.01
DF	1,5 NS	1,5 NS	1,5 NS	1,5 NS

Key: 1 - Tuberculotic patients, 2- Control subjects.

Table 5.74 Giving the means ± lSD for the amplitude of the CI CII configuration for pattern onset-offset stimulation in 6 tuberculotic patients and 6 control subjects.

Subject Grp	PO/N 56' B/Y C1 C11 (uV)
1	3.64±3.14/3.64±3.15
2	6.85±2.85/6.43±2.55
F Value for Eyes DF	0.44 1,5 NS
F Value for Groups DF	3.46 1,5 NS
F Value for Interaction DF	0.12 1.5 NS

Table 5.75 Giving the means ± 1SD for the amplitude of the C1 C11 configuration for pattern onset-offset stimulation in 6 tuberculotic patients and 6 control subjects.

eye at 56' (no response from the left eye) and no discernible response at 27'. No discernible colour responses were elicited for 56' checks for either type of stimulation. On the repeat investigation, delayed VERs were obtained for 2^{o} and 56' pattern reversal black/white stimulation from either eye, with discernible but delayed VERs from the right eye only at 27'. For pattern onset-offset 56' stimulation, the latency for the right eye decreased by 15 ms and a response was now obtained from the left eye (however, it was delayed in comparison to the right eye). A similar type of response was seen for 27' (Figure 5.28, 5.29). In spite of considerable improvement shown in the responses for both pattern reversal and onset-offset stimulation, the VERs still remained fairly low amplitude.

5.2.2 Psychophysical Results

Visual Fields

It was only possible to obtain visual fields and flicker fusion measurements on 3 subjects (DS, HS, EH) as 2 patients could not be easily moved and the other was unable to speak English. Of the 3 subjects who were tested, 2 (HS,EH) demonstrated reduced macular thresholds to colour stimulation and white light whilst the third subject (DS) yielded macular thresholds which were within normal limits, but those for the left eye were at the lower limits for normality. This interocular difference was also reflected in his VAs and VERs to the smaller check size.

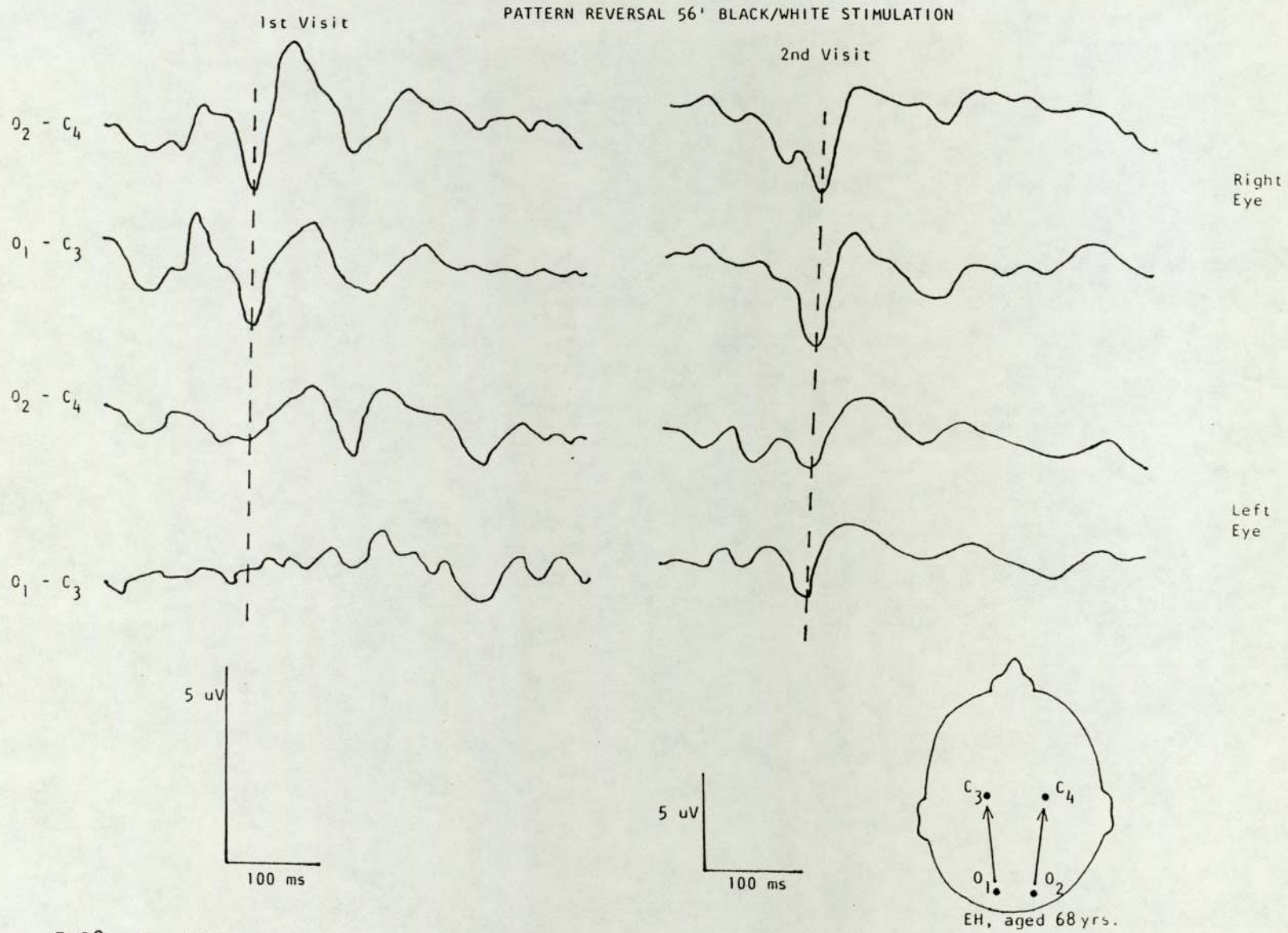


Figure 5.28 The VERs to pattern reversal 56' black/white stimulation in a patient with Ethambutol toxicity; on the first investigation the responses from the right eye showed a delay in the P2 component whilst the responses from the left eye were indiscernible, however, on the second investigation, each eye demonstrated delayed responses with those from the left eye being of lower amplitude

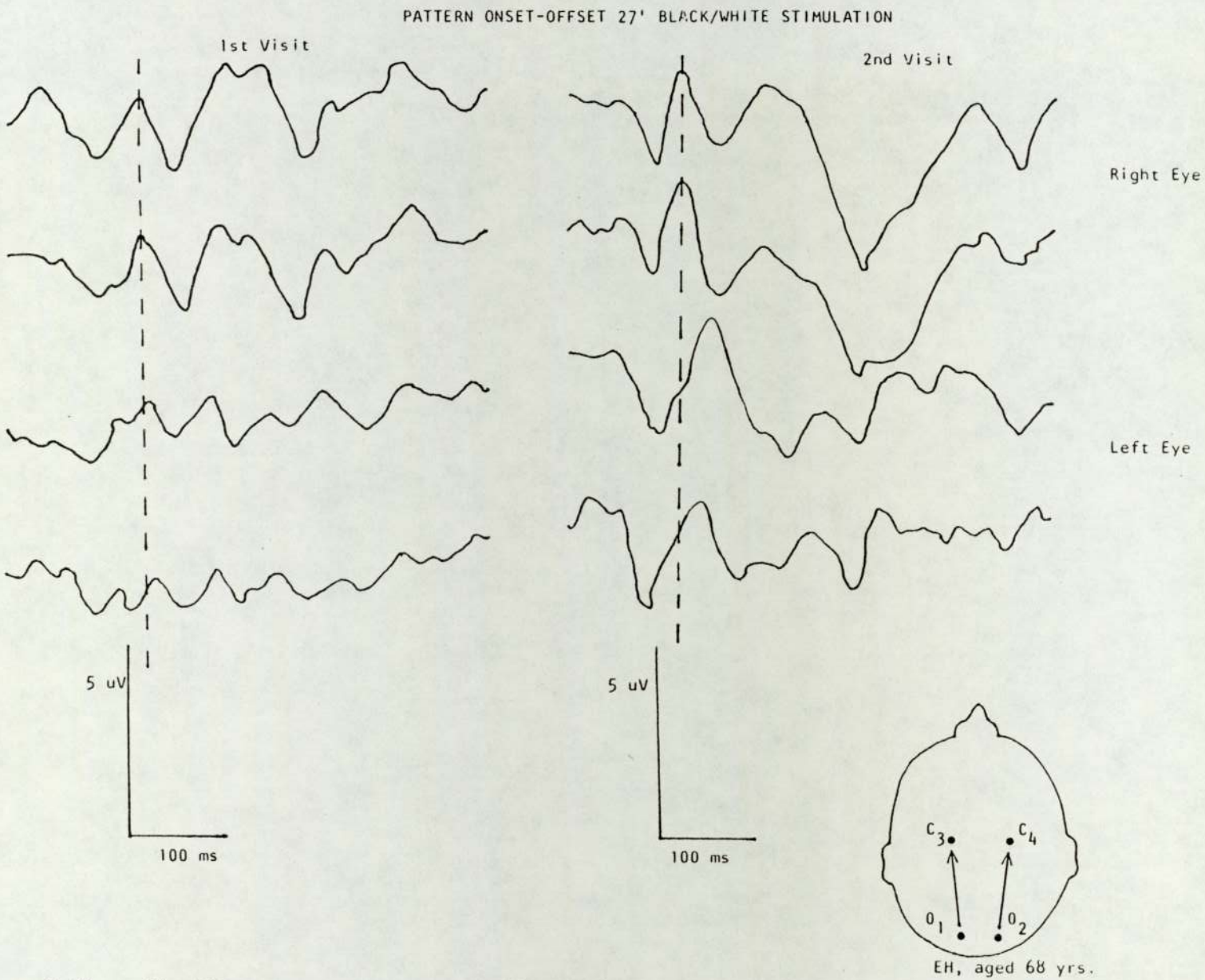


Figure 5.29 The VERs to pattern onset-offset 27' black/white stimulation in a patient with Ethambutol toxicity; on the first investigation, discernible CII components are seen in the responses of the right eye but the responses from the left eye are indiscernible. However, on the second investigation each eye demonstrated discernible responses, with the right eye revealing an improved CII latency, hence resulting in an interocular difference in latency

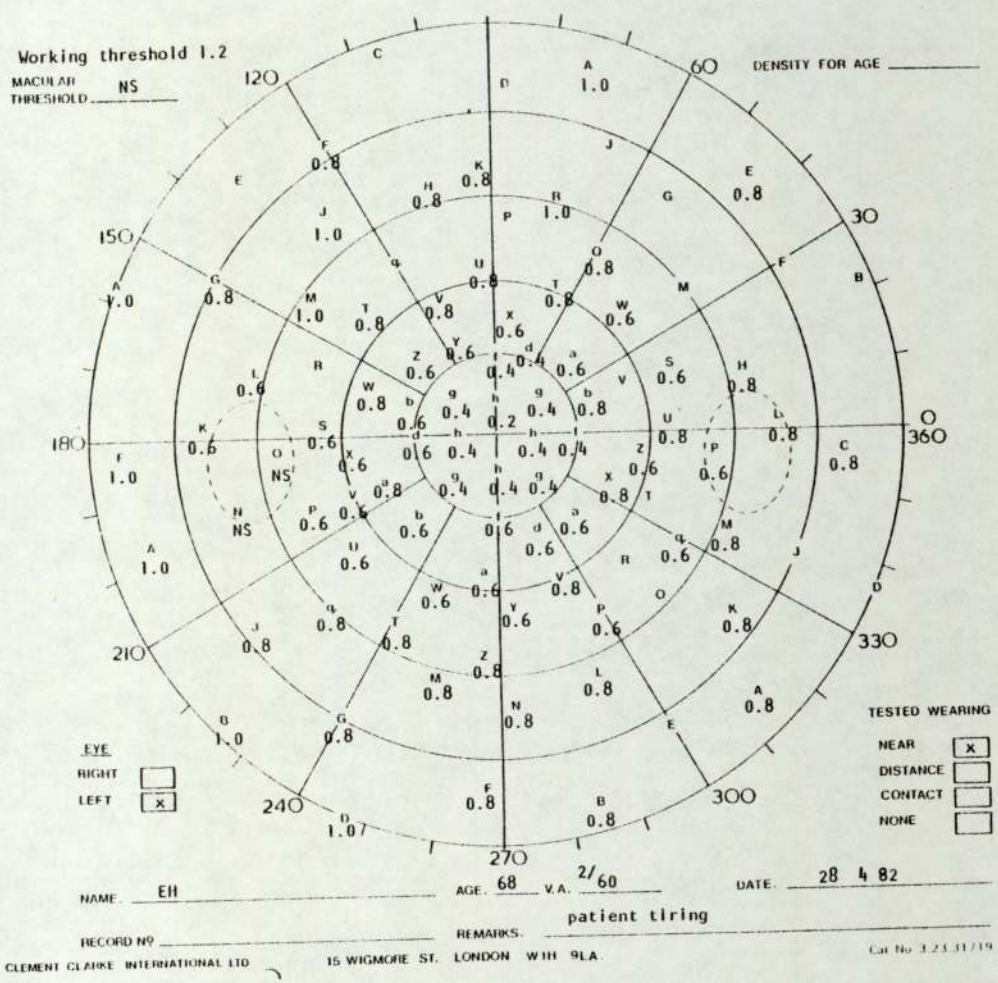
Visual fields were ~~were~~ performed on 2 subjects (DS, EH), with one subject (EH) showing a generalised depression which is worse in the central area, especially from the left eye (Figure 5.30). The other subject (DS) demonstrated an elongation of the blind spot in the left eye but a normal visual field in the right eye. If this patient had been examined according to the standard method, this reduction in sensitivity would not have been observed.

On the repeat investigation, subject (HS) revealed improved macular thresholds to white and coloured lights (from 0.6 to 1.0 for red; 1.0 to 1.4 for green; from "not seen" to 0.4 for blue; from 1.4 to 2.0 for white). Subject (EH) also revealed an improvement to all visual field parameters, more so in the right eye (Figure 5.31).

The Fusion Thresholds to Flicker Stimulation at 3, 10 and 30 Hz

The log sensitivities to flicker fusion are within normal limits for each eye in one subject (DS) but the interocular difference which is noted for the other tests is not seen in this test. In the other 2 subjects (HS, EH), there are abnormal values at all three frequencies with subject (EH) being unable to discern any flicker modulation at any frequency for the left eye.

Subjects (HS, EH) who were repeated showed an increase in their CFF values. The CFF values for subject (HS) increased from 12 Hz to 30 Hz in each eye whilst that for subject EH increased from 6 to 14 Hz in the right eye, and the left eye (from which no value could be previously obtained) now yielded a value of 8.5 Hz.



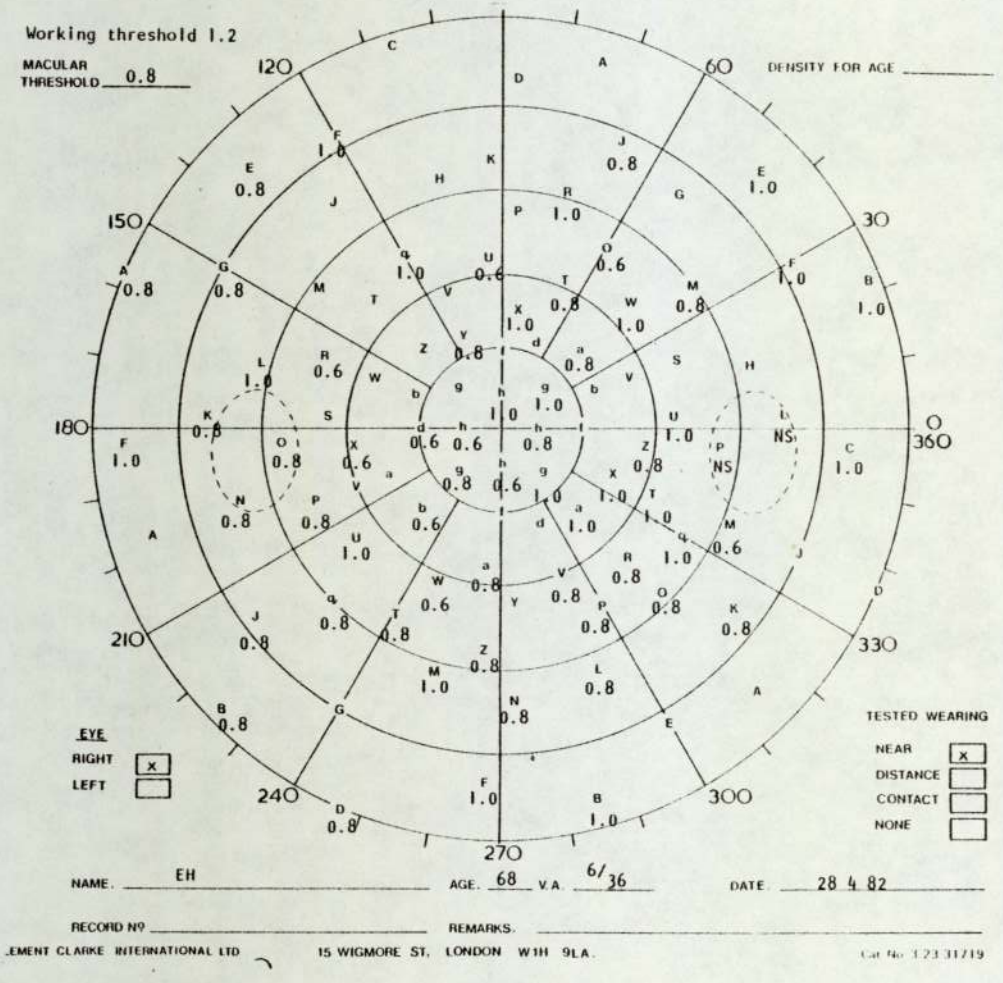
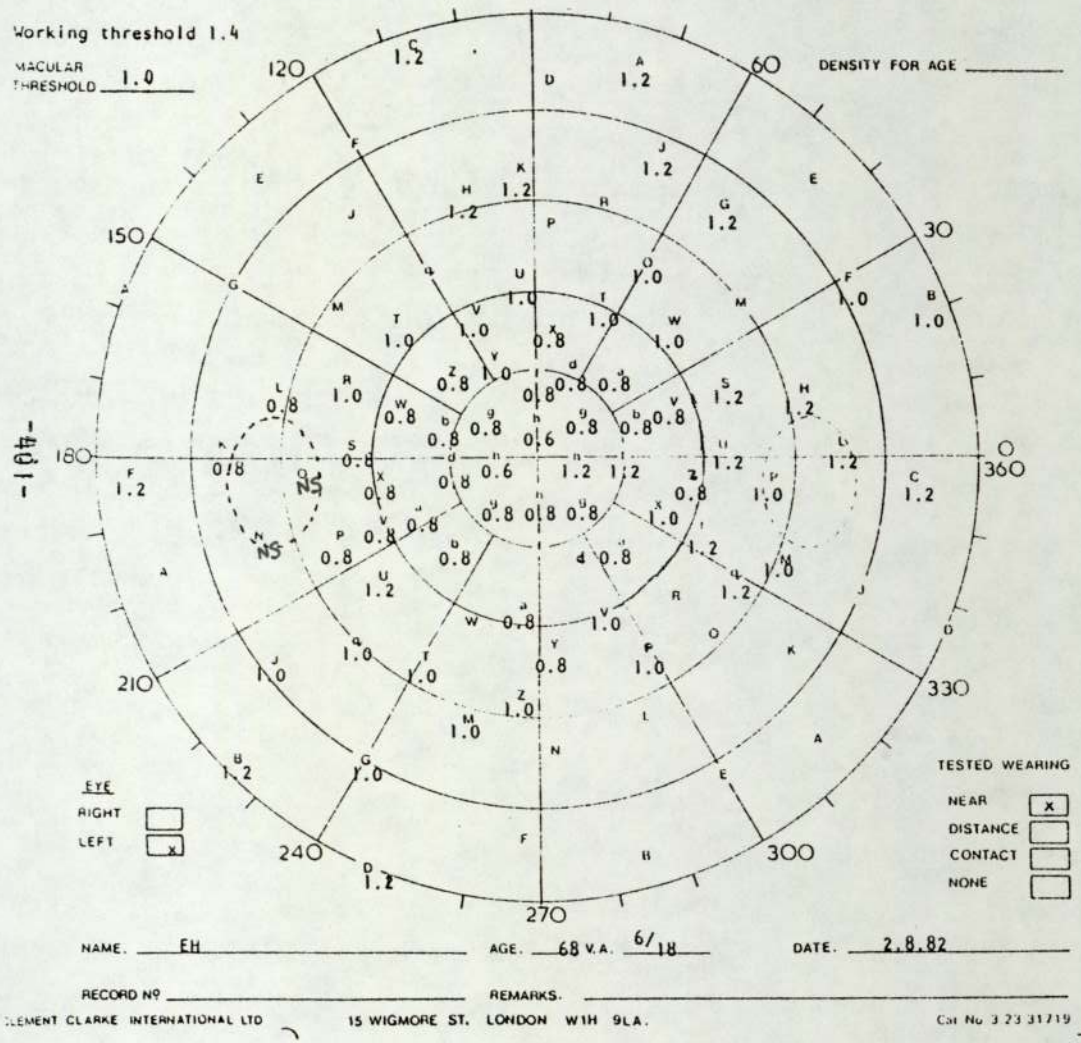


Figure 5.30

The Friedmann visual field plots of a subject suffering from Ethambutol toxicity, showing a generalized depression which is worse in the central area



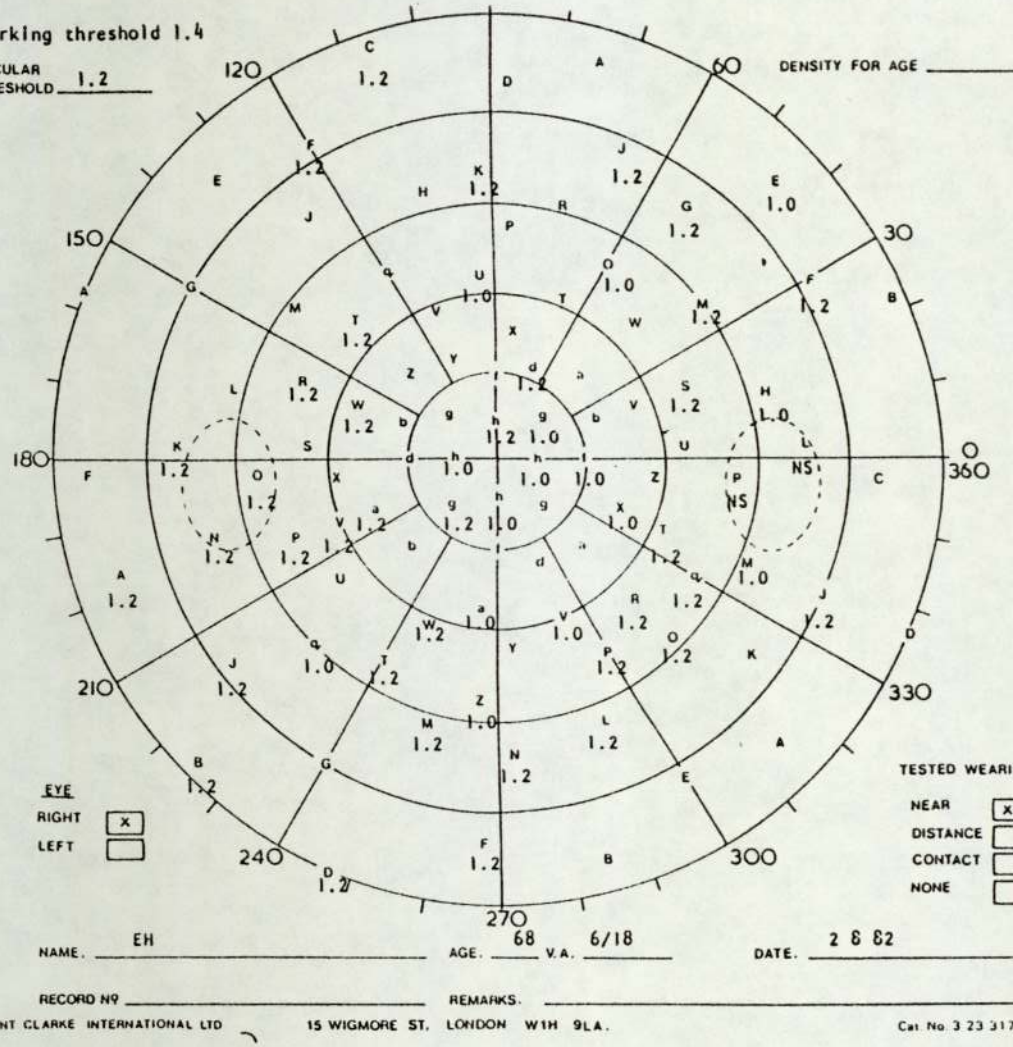


Figure 5.31

The Friedmann visual field plots of the same subject in Figure 5.30. It can be seen that there is an improvement in the light threshold values in comparison to those of the first investigation, although a reduction in sensitivity is still present

There is a marked improvement in the log sensitivities for all frequencies in each eye for subject (HS) for the right eye, from 0.6433 to 0.9994 at 3 Hz; from 0.7240 to 1.2255 at 10 Hz; from no value to 0.5890 at 25 Hz) and for subject EH (for the right eye, from 0.9205 to 1.452 at 3 Hz; from 0.862 at 6 Hz to 0.8955 at 10 Hz). For the latter subject, flicker thresholds could now be obtained from the left eye (at 3Hz, 0.7386 and at 6 Hz, 0.7361).

Although only 2 subjects have been repeated, it would appear that there is a high frequency attenuation which would agree with the findings of Meyer et al. (1974) who reported this in patients with Ethambutol toxicity. They plotted the de Lange curves for a 1^{o} test spot and postulated that the lesion is perifoveal rather than foveal.

5.3.3 General Discussion and Summary of Findings

There was an improvement in the VAs, pattern VERs, MTs, VF scores and log flicker sensitivities for the two subjects who were repeated. Although subject (HS) was examined 19 months after his initial investigation and his VA improved from 6/18 to 6/9 in each eye, it is still clear that the recovery is incomplete especially for the VERs. Subject (EH) also showed considerable improvement after 4 months although the test parameters were still far from being normal.

Unfortunately, it was only possible to obtain dose levels of the drugs used for tuberculotic therapy for one patient (MT) who was visually affected. From Table 5.68, it can be seen that the dosages

of Ethambutol (13.6 mg/kg) and Isoniazid (4.6 mg/kg) are well within the recommended levels, however, this patient has impaired renal function which could account for her visual deterioration*.

The VER investigation revealed both delayed latencies and reduced amplitudes in both the visually unaffected and affected patients. The delayed latencies could be associated with the findings of Schmidt (1966) in the monkey, whereby after the administration of larger doses of Ethambutol, demyelinating lesions were observed initially in the optic chiasma and then the optic nerve followed by a manifestation of widespread central nervous system (CNS) damage. However, fairly low doses of Ethambutol and Isoniazid have been administered to the visually unaffected patients in this study which would make the proposition of demyelination less likely for the delayed VER latencies seen in these patients. Schmidt (1966) postulated that at this stage of intoxication the effect of the drugs is irritative rather than destructive. McDonald (1974) suggested that other processes besides demyelination can play a part in the obstruction of conduction in lesions of the CNS, such as oedema. However, if demyelination does occur, especially in the affected patients, it has been suggested that remyelination is possible in lesions of the CNS (McDonald 1974).

In addition, to the increased VER latencies, reduced amplitudes (especially in the affected patients) have been observed. Ikeda et al. (1978) postulated that low amplitudes are associated with a nutritional or toxic malfunction which could affect the enzymic and

* The dosages of two other subjects (EH, CS) were obtained. The dose levels of 13.1 mg/kg and 14.6 mg/kg Ethambutol and 3.9 mg/kg and 3.2 mg/kg Isoniazid respectively were also well within the recommended levels. However, subject EH was hypertensive and asthmatic.

and transport processes of the relay cells and axons. This postulation would be in accordance with the proposition of Yolton, (1981) that the chelation of zinc by Ethambutol or Isoniazid, makes the zinc unavailable for axoplasmic transport resulting in optic or retrobulbar neuritis. On the basis of these studies it is proposed that if subclinical changes are present as indicated by the electrophysiological results, then the accumulated deficits eventually give rise to supra-threshold levels, leading to abrupt and severe symptoms. In the visually unaffected patients whose Ethambutol serum levels were taken, there does not seem to be any correlation between this parameter and the P_2 component for flash stimulation. The 3 subjects (4T, 6T, 12T) who yielded abnormal results, all had low serum levels (1.4, 2.4, 4.6 mg/l respectively) and no record of abnormal renal function. However, it is interesting to note that one of these subjects (SL) had been receiving Ethambutol for the longest period ($5\frac{1}{2}$ months). In the visually affected patients it is also noted that 2 patients (DS, HA) suffer from diabetes and one (MT) has impaired renal function.

5.5.4 Comparison of Results of Visually Symptomless Chronic Alcoholic and Tuberculotic Patients

The results which have been obtained from the visually symptomless patients in the tuberculotic group and the chronic alcoholic group indicate that the mechanisms of action of the tuberculotic drugs (especially Ethambutol) upon the visual system differs from the action of alcohol and/or tobacco.

In the case of Ethambutol, and possibly Isoniazid therapy, the more significant changes seen for the flash VERs than for the pattern VERs would suggest that these drugs have a more generalised effect on the visual system. On the otherhand, the results for the chronic alcoholics indicate that the effect of alcohol and/or tobacco is more specific to the macular region as the macular thresholds and VERs to the small check and field size have been the most affected parameters. This would be in accordance with the central or centro-caecal scotomata reported in tobacco-alcohol amblyopes. However, for Ethambutol toxicity, not only central field defects are found but also constricted field defects. This would support the postulation of the more generalised effect of Ethambutol on the visual system.

For both groups of subjects, there is evidence of retinal involvement, although more abnormal results have been produced from the occipital cortical responses. Recent work performed on isolated carp retinas superfused with different concentrations of Ethambutol, indicate that the amacrine and bipolar cells are most likely to be affected by this drug. (Van Dijk and Spekreijse 1983).

5.6 Data on Patients Suffering from "West Indian Amblyopia"

Eight
~~Seven~~ patients (4 males, 4 females, $\bar{x}$ = 50 1±13.8 yr) who have been diagnosed as having "West Indian Amblyopia" have been examined and their results have been compared to those of 8 age-and-sex matched control subjects (Table 5.76).

5.6.1 Electrophysiological Results

Electroretinograms

The dark-adapted and photopic ERGs of one subject (AL) were of low amplitude and practically obliterated except for a wave which appears to be an A wave (Figure 5.32). The photopic ERG of subject (SH) did not reveal any OPs for the right eye which is the eye with the worse VA. The data for the other subjects is within normal limits for the parameters measured (Table 5.77).

Visual Evoked Responses

On analysing the latencies of the VERs using the Fisher-Yates test, no significant difference has been observed for flash stimulation. Nevertheless, one subject (AL) had indiscernible responses and another (SH) demonstrated a PNP response in the right eye only. Whereas the data for pattern reversal 56' black/white and blue/yellow stimulation gave a significance level of 4%, it was increased to 1% for red/green. Pattern reversal 14' black/white and red/green stimulation reveal highly significant results ($p<0.003$) (Table 5.78).

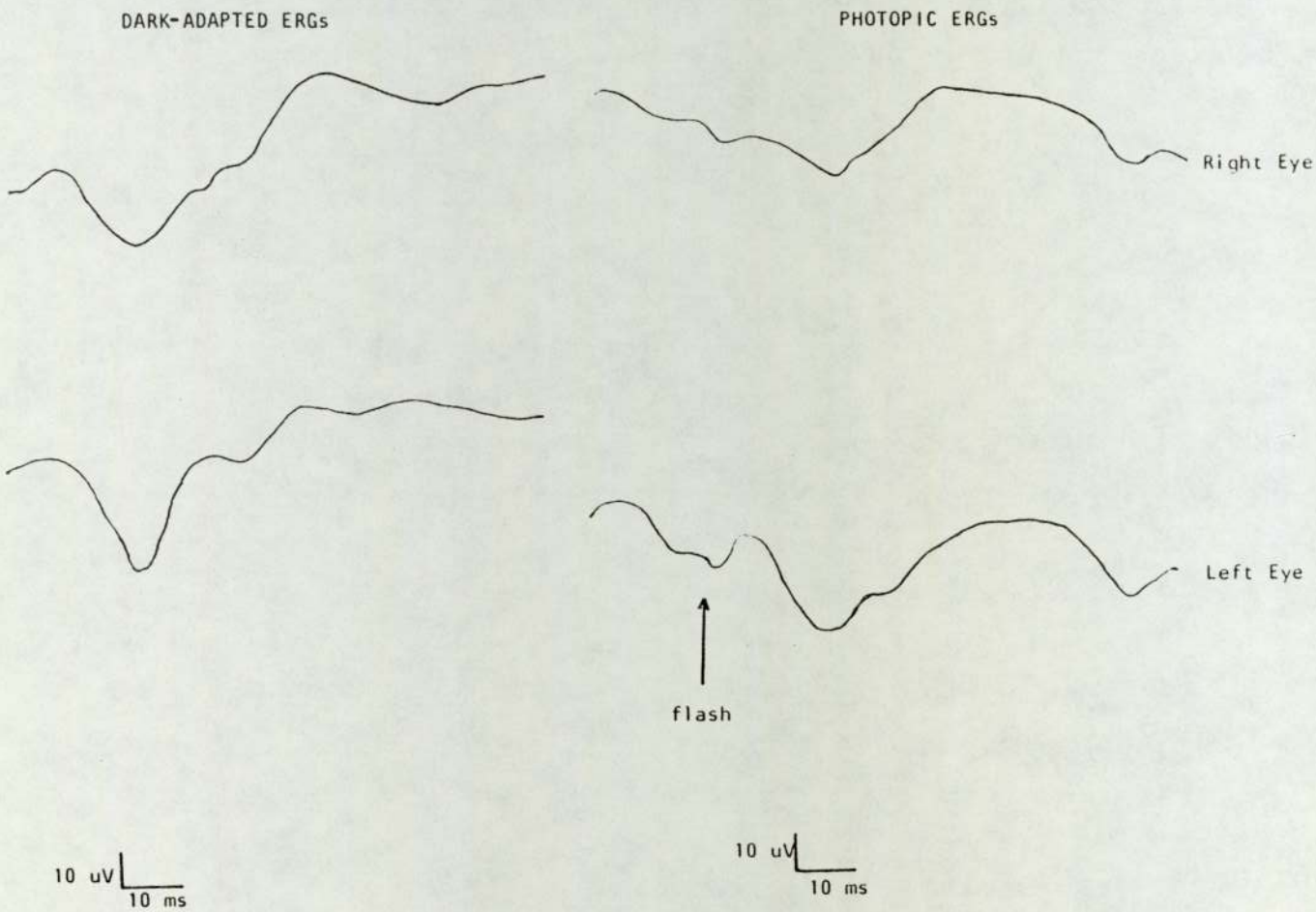


Figure 5.32 The dark-adapted and photopic ERGs in a subject with West Indian amblyopia whose responses were poorly formed

Subject	Age (Yr.)	Sex	Visual Acuity	Pupil Size	Ocular Changes	Onset of Visual Symptoms/Other Illnesses	Period of Time In Britain	Ingestion of Foodstuffs
SD	21	M	6/36 N24 6/36 N24	5	Mild bilateral optic disc pallor	12 mth/ Hearing loss	Born in Britain	Never consumed cassava, yams or bush teas. 20 cig/day Occasional drinker.
JA	44	F	6/6- N6 6/6- N6	4	Early granulation around each macula	6 mth	15 years	Ate cassava and yams until 15 years ago. Non-smoker Teetotaller.
CM	48	M	6/36 N24 6/18-1 N14	4	Bilateral temporal optic disc pallor; pigmentation on R disc;peripapillary pigmentation in left eye.	4 years	26 years	Ate cassava until 26 years ago. Non-smoker Drinks beer or spirits on social occasions.
DD	50	F	6/24 N10 6/18+2N10	4	Mild bilateral temporal optic disc pallor.	32 years	25 years	Ate cassava, yams and bush teas occasionally Non-smoker Teetotaller.
DC	55	F	6/36 N18 6/36+1N14	4	Mild bilateral temporal optic disc pallor; bilateral macular pigmentation.	10 years	29 years	Never consumed cassava, bush teas; ate yams. Non-smoker Teetotaller.
VH	57	M	6/18+2 N8 6/9-2 N8	3.5	Early cortical lens changes.	2 months	22 years	Ate cassava often until 22 years ago, now only about once per year. Drinks 1 or 2 cups of peppermint tea twice per week. Non-smoker. Drinks spirits about once per week.
AL	59	M	6/60<N48 6/60<N48	2.5	Bilateral temporal optic disc pallor; pigmentation between disc and macula; Early cortical lens changes.	7 years/Hypertension.	20 years.	Ate cassava, yams and bush teas often until coming to Britain, now he rarely consumes them. 20 cig/day Drinks about 1.1 l lager/day.
SH	67	F	6/36 N8 6/18 N8 with high add for near	2.5	Pale optic discs. L > R	2 years	26 years	Non-smoker, Occasional drinker.

Table 5.76 Giving the particulars of the patients suffering from "West Indian Amblyopia".

Subject Group	A(ms) R	A(ms) L	B(ms) R	B(ms) L	AB(uV) R	AB(uV) L	A(ms) R	A(ms) L	B(ms) R	B(ms) L	OP1(ms) R	OP1(ms) L	OP2(ms) R	OP2(ms) L	AB(uV) R	AB(uV) L
1	25.86±1.11/ 25.98±1.10		48.73±1.80/ 49.31±2.06		220.10±61.33/ 216.99±57.16		19.76±1.30/ 19.45±1.23		43.63±2.45/ 43.47±1.79		24.64±1.55/ 24.29±1.69 No OP in 1 Sub		30.83±1.37/ 31.17±1.59 No OP in 2 Subs		60.70±23.32/ 62.71±22.82	
2	25.40±1.67/ 25.36±1.82		49.29±1.93/ 49.13±1.82		246.61±58.36/ 245.67±58.15		20.31±0.96/ 20.56±1.59		44.00±1.55/ 44.29±0.99		25.00±1.56/ 24.50±1.56		31.67±1.31 31.58±1.10		86.00±13.58/ 90.07±17.63	
F value for Eyes DF	0.02 1,7	NS	0.84 1,7	NS	0.13 1,7	NS	0.02 1,7	NS	0.03 1,6	NS	0.04 1,6	NS	0.22 1,5	NS	0.67 1,6	NS
F value for Groups DF	0.97 1,7	NS	0.02 1,7	NS	1.00 1,7	NS	2.11 1,7	NS	1.41 1,6	NS	0.25 1,6	NS	0.42 1,5	NS	4.89 1,6	NS
F Value for Interaction DF	0.09 1.7	NS	0.93 1,7	NS	0.03 1,7	NS	2.30 1,7	NS	1.60 1,6	NS	1.28 1,6	NS	0.91 1,5	NS	0.21 1,6	NS

Key: 1 - West Indian amblyopes, 2- Control subjects.

Table 5.77 Giving the means ± ISD for the components of the dark-adapted and photopic ERGs in 8 West Indian amblyopes and 8 control subjects.

Type of Stimulus	Right Eye	Control Subject	West Indian Amblyope	Significance Level	Left Eye	Control Subject	West Indian Amblyope	Significance Level
Flash	Normal	8	5		Normal	8	5	
	Abnormal	0	3	NS	Abnormal	0	3	NS
PR 56' B/W	Normal	8	4		Normal	8	4	
	Abnormal	0	4	$p<0.038$	Abnormal	0	4	$p<0.038$
PR 14' B/W	Normal	8	0		Normal	8	0	
	Abnormal	0	8	$p<0.003$	Abnormal	0	8	$p<0.003$
PR 56' R/G	Normal	8	3		Normal	8	3	
	Abnormal	0	5	$p<0.013$	Abnormal	0	5	$p<0.013$
PR 14' R/G	Normal	8	0		Normal	8	0	
	Abnormal	0	8	$p<0.003$	Abnormal	0	8	$p<0.003$
PR 56' B/Y	Normal	8	4		Normal	8	4	
	Abnormal	0	4	$p<0.038$	Abnormal	0	4	$p<0.038$

Key:- PR - Pattern reversal; B/W - Black/White; R/G - Red/Green; B/Y - Blue/Yellow

TABLE 5.78 Showing the number of P_2 peak latencies which fall within or beyond normal limits for 8 control subjects and 8 West Indian Amblyopes.

Pattern onset-offset 56' black/white, blue/yellow and red/green stimulation gave significant results at the 4%, 1% and 0.3% levels respectively. Like pattern reversal, the results to onset-offset 14' black/white and red/green stimulation are highly significant ($p<0.001$ for the right eye and $p<0.003$ for the left eye in both cases), (Table 5.79).

The amplitudes of the N_2P_2 configuration have been analysed by two-way ANOVA. For flash stimulation a significant difference has been obtained which reflects the general low amplitude responses seen in this group ($p<0.01$) (Table 5.80, Figure 5.33).

For pattern reversal 56' black/white and blue/yellow stimulation, the significance level is 5% whilst for red/green stimulation, it is 1% For pattern reversal 14' black/white and red/green stimulation, the results are also highly significant ($p<0.01$). Unlike pattern reversal 56' stimulation, pattern onset-offset 56' stimulation has not revealed any marked difference for black/white and coloured stimulation, demonstrating that generally the amplitudes of the pattern reversal responses in patients tend to be lower than those for onset-offset responses. However, there is a marked difference for onset-offset 14' black/white and red/green stimulation ($p<0.01$) (Table 5.80-5.83).

5.6.2 Psychophysical Results

Visual Fields

The macular thresholds for red, green and white and the visual field scores are markedly different from those of the controls

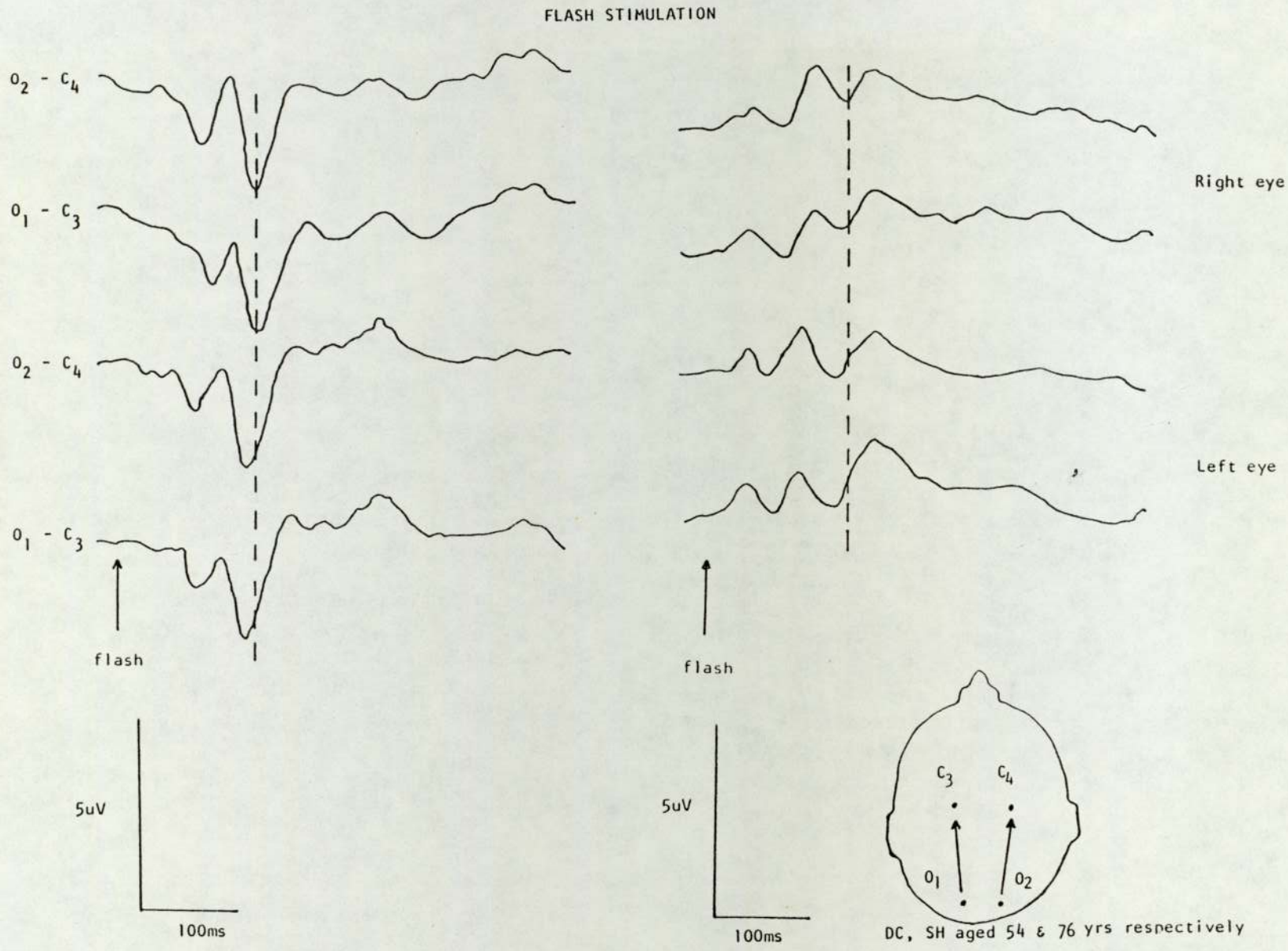


Figure 5.33 The VERs to flash stimulation in two patients with West Indian amblyopia whose responses were of low amplitude, especially in the second subject

Type of Stimulus	Right Eye	Control Subject	West Indian Amblyope	Signif-icance Level	Left Eye	Control Subject	West Indian Amblyope	Signif-icance Level
P O/N 56' B/W	Normal	8	4		Normal	8	4	
	Abnormal	0	4	p<0.038	Abnormal	0	4	p<0.038
P O/N 14' B/W	Normal	7	0		Normal	8	0	
	Abnormal	1	8	p<0.001	Abnormal	0	8	p<0.003
P O/N 56' R/G	Normal	8	1		Normal	8	2	
	Abnormal	0	7	p<0.003	Abnormal	0	6	p<0.003
P O/N 14' R/G	Normal	7	0		Normal	8	0	
	Abnormal	1	8	p<0.001	Abnormal	0	8	p<0.003
P O/N 56' B/Y	Normal	8	3		Normal	8	3	
	Abnormal	0	5	p<0.013	Abnormal	0	5	p<0.013

Key:- P O/N - Pattern onset/offset; B/W - Black/White; R/G - Red/Green; B/Y - Blue/Yellow.

TABLE 5.79 Showing the number of CII peak latencies which fall within or beyond normal limits for 8 control subjects and 8 West Indian Amblyopes.

Subject Grp	PR 56' B/Y		Flash	
	N_2P_2 (uV)		N_2P_2 (uV)	
1	1.45±1.66/1.57±1.70		1.73±0.90/1.51±0.86	
2	3.27±0.84/3.31±1.08		4.93±2.03/5.00±2.74	
F Value for Eyes DF	0.30 1,7	NS	0.12 1,7	NS
F Value for Groups DF	5.59 1,7	p<0.05 NS	15.97 1,7	p<0.01
F Value for Interaction DF	0.08 1,7	NS	0.30 1,7	NS

1 - West Indian Amblyopes, 2 - Control Subjects

Table 5.80 Giving the means ± 1SD for the amplitude of the N_2P_2 configuration for flash and pattern reversal stimulation in 8 West Indian amblyopes and 8 control subjects.

Subject Grp	PR 56' B/W	PR 14' B/W	PR 56' R/G	PR 14 R/G
	N_2P_2 (uV)	N_2P_2 (uV)	N_2P_2 (uV)	N_2P_2 (uV)
1	2.19±1.60/2.43±2.00	0.51±1.12/0.40±1.14	1.49±1.36/1.87±1.29	0.40±1.12/0.42±1.19
2	5.89±2.78/5.16±2.12	4.05±0.93/4.71±1.98	3.83±1.15/3.67±0.88	3.35±0.98/3.33±0.48
F Value for Eyes DF	1.14 1,7 NS	0.86 1,7 NS	0.49 1,7 NS	3.91×10^{-4} 1,7 NS
F Value for Groups DF	8.47 1,7 p<0.05	38.47 1,7 p<0.01	13.43 1,7 p<0.01	26.50 1,7 p<0.01
F Value for Interaction DF	8.40 1,7 NS	1.54 1,7 NS	1.37 1,7 NS	0.04 1,7 NS

Key: 1 - West Indian Amblyopes, 2 - Control subjects, B/W - Black/White, R/G - Red/Green, B/Y - Blue/Yellow

Table 5.81 Giving the means ± 1SD for the amplitude of the N_2P_2 configuration for pattern reversal stimulation in 8 West Indian amblyopes and 8 control subjects.

	PO/N 56' B/W	PO/N 14' B/W	PO/N 56' R/G	PO/N 14' R/G
Subject Grp	C1 C11 (uV)	C1 C11 (uV)	C1 C11 (uV)	C1 C11 (uV)
1	3.62±2.45/3.90±2.25	0.39±1.09/0.36±1.03	3.19±3.01/2.79±2.62	Indiscernible responses for all subjects.
2	5.48±3.14/5.71±3.44	6.19±2.93/6.43±2.39	5.50±1.55/6.19±2.22	5.81±1.87/5.88±2.46
F Value for Eyes DF	0.37 1.7 NS	0.46 1.7 NS	0.34 1.7 NS	Not Analysed
F Value for Group DF	1.05 1.7 NS	46.11 1.7 p<0.01	4.87 1.7 NS	
F Value for Interaction DF	8.88×10^{-3} 1.7 NS	0.83 1.7 NS	4.11 1.7 NS	

Key: PO/N - Pattern onset-offset

Table 5.82 Giving means ± 1SD for the amplitude of the C1 C11 configuration for pattern onset-offset stimulation in 8 West Indian amblyopes and 8 control subjects.

Subject Grp	PO/N 56' B/Y C1 C11 (uV)
1	4.23±2.82/5.18±2.93
2	6.24±1.92/6.07±2.01
F Value for Eyes DF	1.41 1,7 NS
F Value for Groups DF	3.27 1,7 NS
F Value for Interaction DF	1.28 1,7 NS

Table 5.83 Giving means ± 1SD for the amplitude of the C1 C11 configuration for pattern onset-offset stimulation in 8 West Indian amblyopes and 8 control subjects.

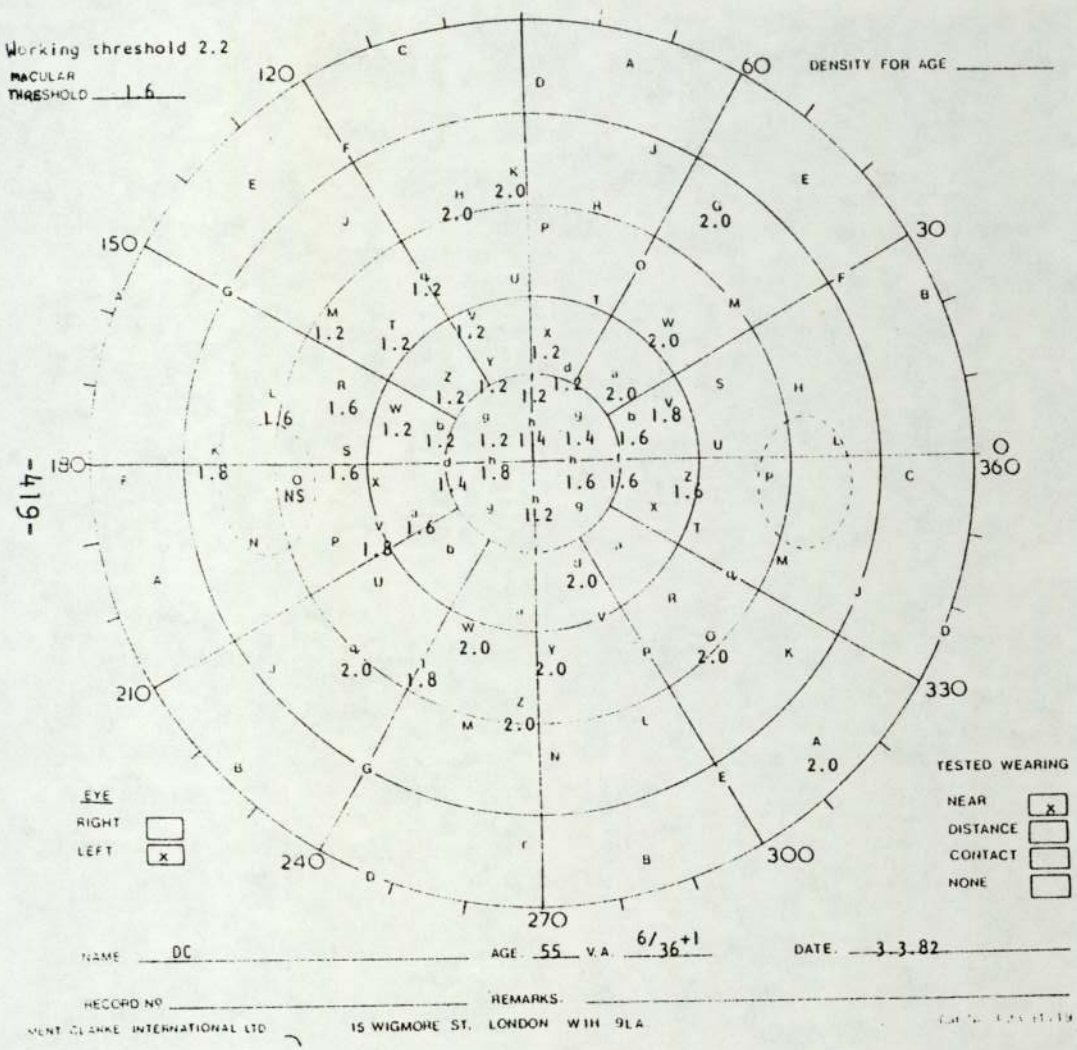
($p<0.01$, Table 5.84). For the macular thresholds to blue light 2 subjects (AL, SH) were unable to perceive the light at all. This could be partly because of the high density of the blue filter, hence requiring high transmissions (therefore a low log sensitivity) especially in the elderly patients, such as subjects (AL, SH).

On comparing the macular thresholds for the right and left eyes of the West Indian amblyopes to the range of macular thresholds for normal subjects of the appropriate age group, the number of patients whose thresholds fall below normal limits are shown in Table 5.85.

Colour of Stimulus	Right Eye	Left Eye
Red	6	6
Green	7	6
Blue	5	3
White	5	6

Table 5.85 Showing the number of West Indian Amblyopes whose Macular Thresholds are below the Normal Range for the Age

The visual fields of these subjects have a generalised depression in sensitivity, with the central field being more affected in some instances, whilst in others there is a more peripheral defect. (Figure 5.34, 5.35).



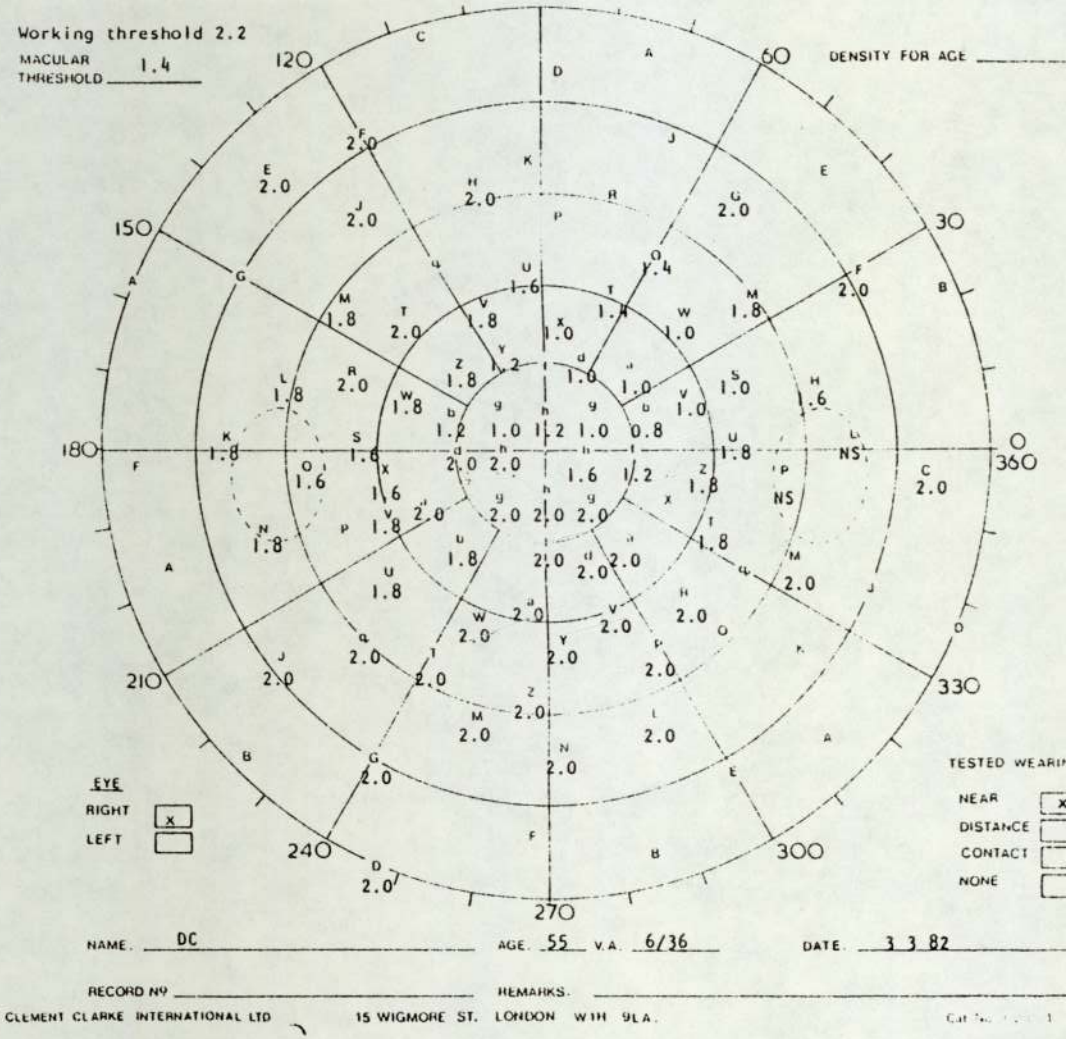
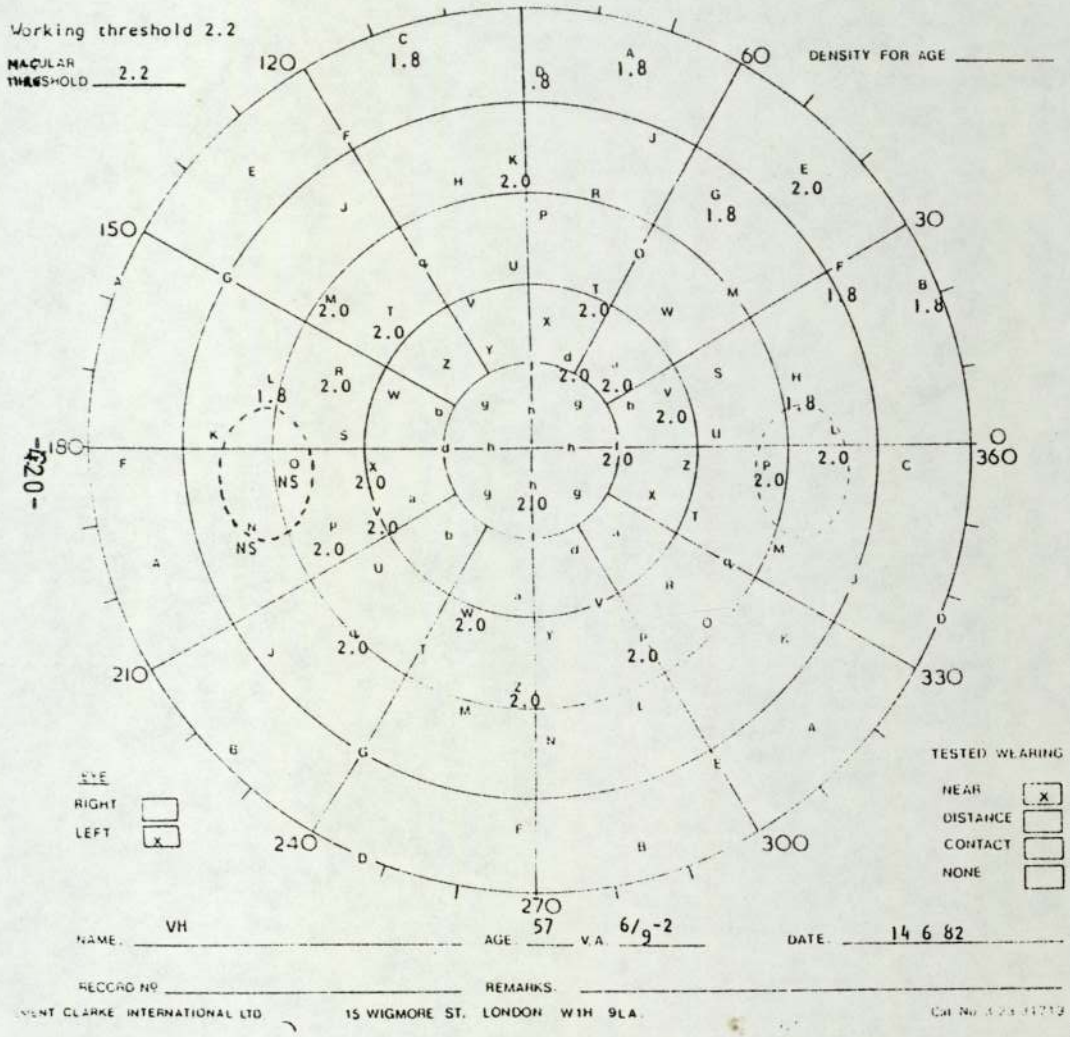


Figure 5.34

The Friedmann visual field plots of a subject suffering from West Indian amblyopia, showing greater depression in sensitivity in the central area



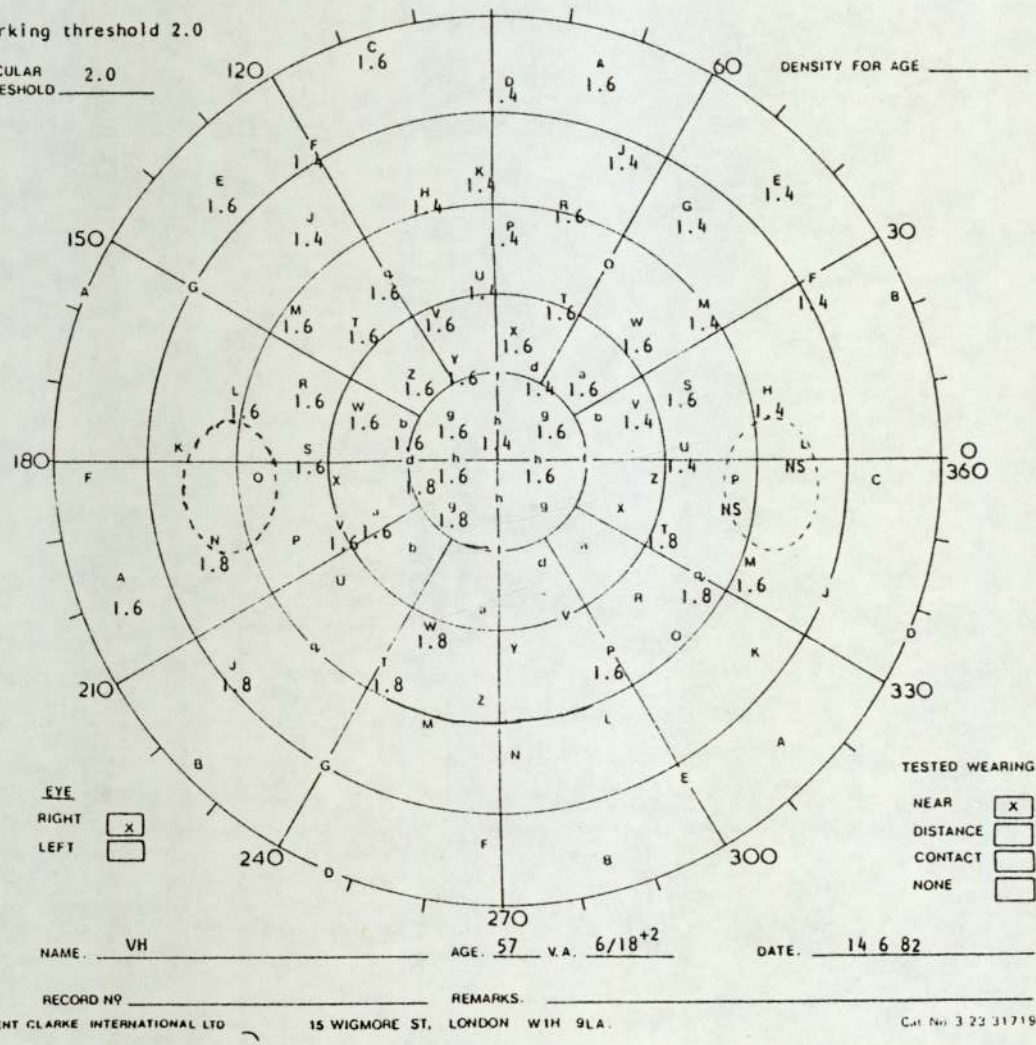


Figure 5.35

The Friedmann visual field plots of a subject suffering from West Indian amblyopia, showing a greater depression in sensitivity in the periphery

Subject Group	MACULAR THRESHOLD (log units)								Visual Field Score (log units)	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L	R	L
1	1.77±0.64/1.85±0.48 (0.8-2.4) (1.0-2.4)		1.63±0.52/1.70±0.47 (1.0-2.4) (1.0-2.2)		1.08±0.40/1.15±0.38 (0.8-1.4) (0.8-1.2)		0.63±0.34/0.70±0.25 2 subjects did not perceive light (NS - 1.0) (NS-0.8)		185.68±36.76/193.33±34.50	
2	2.70±0.15/2.68±0.15 (2.4-2.8) (2.4-2.8)		2.43±0.17/2.50±0.11 (2.2-2.6) (2.4-2.6)		1.80±0.26/1.83±0.20 (1.4-2.2) (1.6-2.0)		0.95±0.18/0.95±0.18 (0.8-1.2) (0.8-1.2)		219.83±15.42/219.65±16.58	
Non zero value (n)	8	8	7	8	8	8	6	6	8	8
T value for R+L Eyes	0	0	0	0	0	0	1.5	1.5	0	0
Between Groups	p<0.01	p<0.01	p<0.05	p<0.01	p<0.01	p<0.01	p<0.05	p<0.05	p<0.01	p<0.01
Non zero value (n)	4		6		4		3		7	
T value for Interocular difference for Grp 1	0		6.5		2.5		0		7.5	
	Unspecified		NS		Unspecified		Unspecified		NS	

Table 5.84 Giving the means ± 1SD and ranges of the macular thresholds and visual field scores in 8 West Indian amblyopes and 8 control subjects.

The Fusion Thresholds to Flicker Stimulation at 3, 10 and 30 Hz

The log sensitivities to flicker fusion have revealed significant differences for 3 and 10 Hz ($p<0.01$) (Table 5.86). However, the results at 30 Hz have failed to achieve significance. (Figure 5.36).

The number of subjects whose log sensitivities are reduced below normal limits for the age are shown in Table 5.87.

Flicker Frequency (Hz)	Right Eye	Left Eye
3	6	6
10	6	5
30	2	2

Table 5.87 Showing the number of West Indian Amblyopes whose Log Sensitivities of the Flicker Fusion Thresholds Fall Below Normal Limits for Age

5.6.3 General Discussion and Summary of Findings

Once more, these results indicate that visual damage occurs at the retinal and post-retinal levels in this disease. The general low amplitude of the VER data would suggest a nutritional or toxic malfunction (Ikeda, et al. 1978) and although it has been postulated that this disease could be due to nutritional and toxic defects, it has been most difficult to isolate any specific substance or group of substances as the primary cause. Three of the 8 patients were both non-smokers and teetotallers, with an additional 2 patients being non-smokers which would not seem to implicate

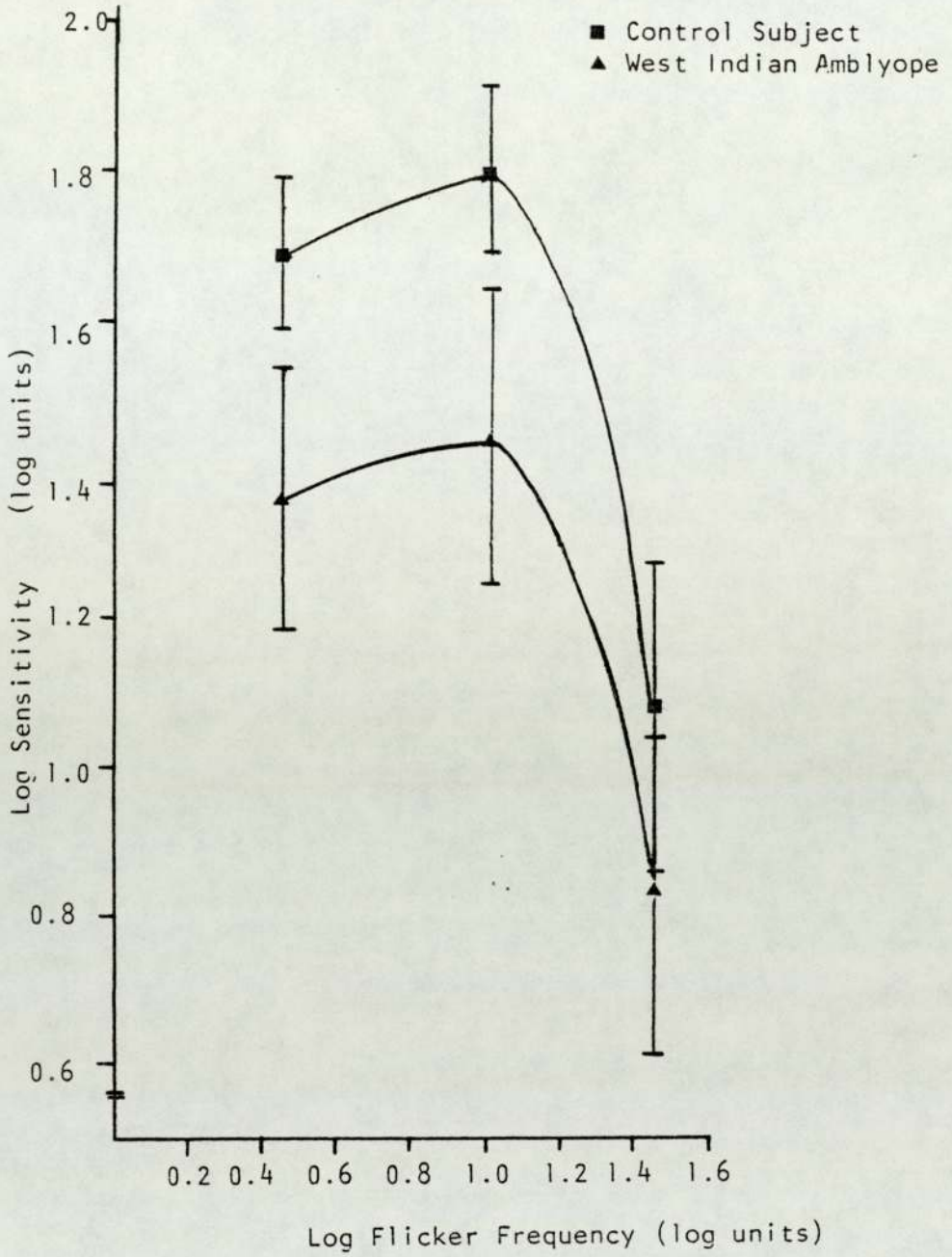


Figure 5.36

Graph showing the means ± SD for log sensitivity of the flicker fusion thresholds in 8 West Indian amblyopes and 8 control subjects.

Subject Group	LOG SENSITIVITY (log units)		
	3 Hz	10 Hz	30 Hz
	R / L	R / L	R / L
1	1.3591 ± 0.1765 / 1.3734 ± 0.1605	1.4439 ± 0.1959 / 1.4360 ± 0.1956	0.8255 ± 0.2145 / 0.8161 ± 0.1876
2	1.6911 ± 0.1032 / 1.6585 ± 0.0754	1.8017 ± 0.1099 / 1.8023 ± 0.1576	1.0624 ± 0.2082 / 1.0773 ± 0.2091
F Value for Eyes DF	0.26 1,7 NS	0. 06 1,7 NS	0.10 1,7 NS
F Value for Groups DF	19.85 1,7 p<0.01	18.16 1,7 p<0.01	5.05 1,7 NS
F Value for Interaction DF	3.21 1,7 NS	0.06 1,7 NS	0.80 1,7 NS

Key: 1 - West Indian Amblyopes, 2 - Control subjects.

Table 5.86 Giving the means ± 1 SD for the log sensitivity of the flicker fusion thresholds in 8 West Indian amblyopes and 8 control subjects.

these substances as causative factors. On a whole, these patients have a fairly long history of subnormal vision which might be a contributing factor to the disappointing response to treatment.

CHAPTER 6

CONCLUSIONS

CONCLUSIONS

There has been a gradual and significant increase in the peak latencies of the A and B waves and OPs, as well as a gradual reduction in the amplitude of the AB configuration of the dark-adapted and photopic ERGs with progressive age changes. Marked changes with increasing age have also been noted for the peak latencies of the VERs to flash and pattern stimulation, however, the amplitudes have not demonstrated this trend. This delay in latency with age is not as gradual as that seen in the ERG, but is seen to occur mostly from the fifth decade onwards. The parameters of the psychophysical tests have also shown significant changes in their values. The logarithmic sensitivities of the macular thresholds to white and coloured lights all revealed a reduction with progressive age which is also reflected in the visual field scores. Similar to the VERs, this decrease in sensitivity takes place more dramatically from the fifth decade and continues to deteriorate with advancing age. The greatest percentage change in the logarithmic sensitivities of the macular thresholds between the youngest and oldest age groups occurred for blue light and least for white light which would indicate a greater deterioration of the colour mechanisms. On considering the logarithmic sensitivities of the fusion thresholds to flicker stimulation, a similar reduction in sensitivity is seen at the low, medium and high frequencies with age. However, this age effect is more marked for the high frequency than for the lower frequencies, beginning to show a definite reduction in sensitivity from the fourth decade, in comparison to the fifth decade for the lower frequencies. In conclusion, it can be said that for both the electrophysiological and psychophysical tests, there is a deterioration in the value of the parameters with the effect of increasing age.

The method of eliciting VERs by pattern onset-offset stimulation has been a more recent development than pattern reversal stimulation and hence, there is not a great deal of clinical data available. In this study, it has been found that the component which appears most consistently is the negative CII component which is alledgedly contour-specific. However, the variability of the results has been considerably greater than that for pattern reversal stimulation, with the CII component either failing to appear or was substantially delayed in 2 visually clinically normal subjects. This was also seen in a congenital colour defective for his black/white responses which should have been within normal limits. It is possible that this response is so specific that cortical mapping is required before it can be used efficiently. However, the results of the repeat study on normal subjects indicate that the responses are consistent at the same electrode positions. It also appears that this method of stimulation is useful in patients who are being repeated, as significant changes have been observed in the results of the visually symptomless tuberculotic patients who have been repeated.

In both groups of visually symptomless patients, that is, the chronic alcoholic group and the tuberculotic group, the VER investigation has produced the most significant results and therefore, it includes the most sensitive testing regime of all the tests used. Although other tests, such as the macular thresholds to red stimulation in the alcoholic group, have yielded markedly different values to those of normal subjects, these values still lie within normal limits, whereas for the VERs, abnormal data has been obtained.

The results of the VER study suggest that the substances, alcohol/tobacco

and Ethambutol affect the visual pathways via different modes of action. Whereas the foveal VERs (that is, to the small check and field size) have been most affected in the chronic alcoholic group, especially to red/green stimulation, it is the VERs to flash stimulation which have demonstrated the most significantly different and abnormal results in the tuberculotic group. Nevertheless, the VERs to pattern stimulation have also shown marked changes in the latter group but at a reduced level. It is therefore indicated that alcohol and tobacco produce their initial damage upon the macular visual fibres, especially to the red/green mechanism which would imply that the sustained cells have been more affected that the transient cells. This is also reflected in the changes in the thresholds to the lower flicker frequencies rather than the high frequency.

On the other hand, Ethambutol seems to have a more generalized effect upon the visual fibres which eventually appears to result in either more peripheral or more central damage as various types of visual field defects have been obtained in the affected patients. Although there is an improvement in the VERs following the cessation of Ethambutol, the values still did not return to their original values in which case, Isoniazid could have a contributing or synergistic effect.

Retinal changes have also been observed to occur in the visually symptomless alcoholic and tuberculotic groups with both the scotopic and photopic systems being affected. However, the VERs have produced more abnormal results that the ERGs in each case which would suggest that the primary damage is posterior to the layers of origin of the B wave and OPs, that is, possibly the inner nuclear layer.

The majority of the VA measurements have been within normal limits in the patients who have demonstrated abnormal VERs in the visually symptomless groups. It would thus appear that subclinical changes could go unheeded if this clinical measure is relied on to give indications of neural damage.

From the results obtained on the chronic alcoholics and tuberculotic patients, it has been shown that the VER investigation is most effective in detecting subclinical changes. This should therefore provide a useful tool for early diagnosis, especially in these two patient groups where the subjects are more likely to be unable to co-operate fully with a battery of more demanding tests. In the former group, the span of attention might be limited in spite of the fact that the patients might have ceased "drinking" some time prior to examination. In the latter group where many of the patients cannot speak the language and are in hospital at the time of examination (hence,no interpreter is available), this type of investigation is very valuable, especially since visual changes have been noted for patients on allegedly safe dose regimens. These results would imply that any patients who are on higher dose regimens or on a lower dose regimen for an extended period of time, should be monitored prior to and during therapy.

In the visually symptomatic patients, it has been found that abnormal results have been obtained in all the tests used. In the case of the tobacco-alcohol amblyopes, both the dark-adapted and photopic ERGs have demonstrated abnormal changes, however, the VER investigation revealed more dramatic changes in all of the subjects. The visual fields showed depressions in all of the patients with more severe reductions in

sensitivity occurring in the more central or centrocaecal areas. Decreased sensitivity to flicker stimulation has been noted at the three frequencies tested. It should be said that although the widely-accepted clinical measure of VA has not revealed itself as the most sensitive test in detecting subclinical changes, it still remains a helpful indicator of visual damage especially since it can be performed quickly and it is easily understood.

From the results of the small number of patients who have been repeated, improvement in the visual functions has been demonstrated although recovery is by no means complete in the approximate three-month period allowed between examinations. Even in the subject who had been receiving Cytamen injections for two years, recovery was still incomplete especially for the VER results. This could be because he did not reduce his tobacco and alcohol consumption, although it did not seem to be excessive.

Similar to the results of the tobacco-alcohol amblyopes, all of the tests have reflected the visual deterioration in the tuberculotic patients suffering from Ethambutol toxicity. Once more, the VERs have demonstrated the damage to the visual pathways more efficiently than the ERGs, with the former responses having noticeably low amplitudes. Unfortunately, the visual fields of only 2 patients could be examined. The visual fields of the patient who was more severely affected, revealed a generalized depression in sensitivity, especially in the more central areas whilst the visual field of the other patient only showed an enlargement of the blind spot in the eye with the affected VA. The other eye remained normal. The flicker fusion thresholds were abnormal in 2 of the 3 subjects examined, with a suggestion of higher frequency

attenuation. In the 2 patients who have been repeated, some improvement has been noted in all of the tests. However, in the patient who was examined over a year after the cessation of Ethambutol, there were still abnormal results for all the tests with the distance and near VAs remaining $^{6}/_{9}$ and N8 respectively. It would therefore appear that recovery is fairly slow and is still incomplete after reasonably long periods.

The patients with "West Indian" amblyopia have revealed ERG as well as VER changes with the latter producing more abnormal results. The visual fields have demonstrated generalized depressions.

The modulation thresholds to flicker stimulation are more affected at the two lower frequencies which would indicate that the sustained system has suffered a greater loss of sensitivity. However, it is difficult to associate these results with the dietary intake of these patients as very often they are vague about their case histories. Nevertheless, the majority of the patients have consumed some of the foodstuffs which have been suggested as causing this disturbance of vision which seems to be of fairly long onset in most of these patients.

In conclusion, out of all the tests used, the VER has been shown to be the most effective in detecting subclinical changes in the visually symptomless groups. This is an encouraging result as it is an objective test and thus requires less patient co-operation. This has been found to be useful in examining many of the non-English speaking population who participated in this project. In all of the three conditions studied, visual changes have been observed at the retinal level as well as higher

up the visual pathways, although there is some indication that the site of primary damage is more likely to be beyond the inner retinal layers. In the affected patients, the tests have complemented each other, in that they have all produced abnormal results although certain tests are more sensitive in showing abnormal changes. In addition to this, certain aspects of a particular test have been more effective in detecting changes in the different conditions studied, for example, flash VER stimulation in monitoring visual changes during Ethambutol and Isoniazid therapy.

Ideas for further development

In view of the findings with red/green pattern VER stimulation in the chronic alcoholics, it is suggested that both black/white and coloured stimulation should be utilized in the investigation of groups of alcoholics who have been affected in different ways, for example, patients with liver disease as opposed to patients with neurological disease (such as Korsakoff's psychosis).

It would be valuable if these tests, which are of an objective nature, could aid in the differentiation of suspected disease in alcoholics at an early stage. Although it has been implicated by the results of this project that it is the foveal VER which is most affected in the chronic alcoholics, it would be beneficial to use various check and field sizes to establish the most useful stimuli for clinical purposes. It is even more important with this type of patient that the least demanding test target is employed for standard recording. As the fusion thresholds to flicker stimulation have revealed significant changes to the lower frequencies, it would be useful to examine the flicker fusion thresholds

at the lower frequencies to a small spectral test spot (whereby the wavelength of the stimulus can be varied throughout the spectrum) on a white background and compare the results to those of the VER study. In addition to this, as the contrast sensitivity function has been found to demonstrate defects of the visual system quite effectively in diseases of various natures, such as multiple sclerosis and Ethambutol toxicity (Regan et al. 1977; Foulds 1981), it would once more be interesting to observe the effectiveness of each of these tests. However, it should be mentioned that the latter two tests require considerable patient co-operation.

It has been found that flash VER stimulation has produced the most significant results in recording the changes during tuberculotic therapy in visually symptomless patients. Since Ethambutol and Isoniazid are also used in the treatment of children, it would be worthwhile observing if these visual changes occur in the younger age groups as well. In addition to this, groups of visually symptomless patients who are receiving different dose levels of Ethambutol or are on the drug for various periods should be examined to note if the visual changes are more severe in certain instances. As the contrast sensitivity function has been found to be useful in detecting visual changes in patients with Ethambutol toxicity (Foulds 1981), it would be valuable to compare the results of visually symptomless patients for both the contrast sensitivity function study as well as the VERs study, although Foulds (1981) found the latter test to be more sensitive in visually affected patients.

As far as West Indian amblyopia is concerned, it is not very easy to give suggestions for visual research as the cause of the disease still remains an enigma. However, it is seen that there is considerable

damage to the visual system in most of the cases tested who seem to have fairly long histories of deteriorating vision. By examining visually symptomless young patients who are known to regularly consume the substances which have been suggested as causing this disease, it might be possible to reveal early subclinical changes, especially if subjects with diets which are thought to be adequate are compared to subjects with diets which are not as substantial.

APPENDIX 1

Reasons for choosing parameters for ERG recording.

1) Dark-adapted ERG

a) It has been found out from previous trials carried out in this laboratory and from other investigations (Galloway, 1975, 1981; Babel et al. 1977; Martin and Heckenlively, 1982) that in order to investigate the scotopic retinal functions, it is not necessary to employ dark adaptation periods as long as those previously used (Karpe, 1945). For this study, a dark adaptation period of 10 minutes was chosen as it was thought that the scotopic system would be sufficiently stimulated so that any defects of this system would manifest themselves.

b) A flash stimulus intensity of 2 was used instead of a higher intensity so as to retard the process of light adaptation. On the otherhand, a lower intensity was not used as some light was lost through the pair of diffuse opal goggles and sufficient stimulation of the retina was required within a small number of sweeps.

c) A small number of sweeps as well as a slow flash rate were employed for the same reason as a low flash intensity, that is to retard the process of light adaptation. However, a sufficient number of sweeps has to be used in order to obtain a reasonable response.

d) From pilot runs it was found that when the gain was set at 100 uV/cm on the EEG machine, in most cases the response was so large that the trace could not be fully displayed; therefore it was decided to adjust the gain to 200 uV/cm.

e) A time constant of 0.3s and a low pass filter of 70 Hz were chosen so that the required frequencies, that is, of the A and B waves, were allowed through for the response whilst any noise was kept to a minimum. The maximum number of points which was available on the computer was used (that is, 1024 points with a sampling rate of 97 us).

f) From the sweep times utilised in previous investigations (Auerbach, 1966; Jacobson et al. 1966; Samson-Dolfus et al. 1966; Babel et al. 1977) it was decided to have an analysis time of 100 ms which allowed an adequate portion of the ERG to be obtained.

2) Photopic ERG

a) No dark adaptation was instituted in this test as it was thought that the retina would be quickly light adapted at intensity 16.

b) Flash intensity 16 was used so as to stimulate the photopic retinal function to its maximum.

c) The red filters were employed for the same reason as in (b). In addition to this, it has been reported that the OPs represent the photopic retinal function more than the scotopic retinal function (Jacobson et al. 1966; Ikeda and Friedmann, 1972; Babel et al. 1977; Korth, 1980), so possibly by using red light these potentials might be enhanced.

d) The frequency of flash stimulation was increased within the rate required for photopic function.

e) The number of sweeps was increased to twenty-five so as to have improved repeatability whilst on the otherhand, the number of sweeps was kept to a minimum so as to reduce the effect of fatigue and time taken to complete the test.

f) The time constant was decreased to 0.15 ms and the low pass filter was increased to 700 Hz so that the OPs with frequencies between 120-140 Hz would be seen in the ERG. However, the time constant was not further shortened because the other waves of the ERG might not be clearly seen.

APPENDIX 1

Stimulus Parameters	ERGs		VERs	
	Photopic	Dark-adapted	Flash	Pattern
Stimulus Intensity	16(9661cd/m^2)	2(1363cd/m^2) dark adaptation for 10 mins.	2(1363cd/m^2)	
Stimulus Colour	Red (Kodak Wratten No. 29; 90% transmission at 680nm)	White	White	black/white - 1200 cd/m^2 red/green - 410 cd/m^2 blue/yellow - 1125 cd/m^2 average of 6 readings taken around fixation spot.
Stimulus Duration	10 us	10 us	10 us	For onset-offset - 150 ms "on", 500 ms "off"
Stimulus Frequency	3 Hz	1 flash every 10 s	2 Hz	For pattern reversal - 2 Hz.
Gain Setting	200 uV/cm	200 uV/cm	100 uV/cm	100uV/cm
Time Constant	0.15 s	0.3 s	0.3 s	0.3s
Low Pass Filter	700 Hz	70 Hz	30Hz	30 Hz

continued/....

Appendix 1 - continued

No. of Sweeps	25	4	50	50
Sweep Time	100 ms	100 ms	500 ms	500 ms
No. of Points	1024	1024	250	250
Sampling Rate	97 us	97 us	2 ms	2 ms
Electrode Linkage	$F8 \rightarrow Fp_2$; $F7 \rightarrow Fp_1$	$F8 \rightarrow Fp_2$; $F7 \rightarrow Fp_1$	$O_2 \rightarrow C_4$; $O_1 \rightarrow C_3$	$O_2 \rightarrow C_4$; $O_1 \rightarrow C_3$

Table 1 giving the stimulus parameters used for ERG and VER recording

APPENDIX 2

Friedmann VFA

Greve (1975) had observed up to a 0.6 log unit difference between the suggested filter density and the individual threshold filter density in 21 subjects between 21 and 30 years old. This result was ascribed to the individual departures from the average pattern of the gradient of sensitivity.

For this study, it was decided that a compromise had to be made between increasing the sensitivity of the visual field examination and the effects of fatigue (possible producing false positives). To do this, the threshold luminances for the 98 points of the VFA were established for 20 normals, 10 being between 30 and 39 years ($\bar{x}$=34.7 $\pm$ 3.1 years) and the other 10 being between 60 and 69 years ($\bar{x}$=64.7 $\pm$ 3.7 years). The infraliminal starting filter density was 2.8 log units which was gradually reduced until all points were seen. The criterion for choosing the initial filter density for each age group, was the highest filter density at which at least one third of the points (32) were seen on the most sensitive charts. (Tables 2,3) This proportion was chosen because in patients with a predominantly central defect or peripheral constriction there could be a reduction in thresholds affecting about 50% of the stimuli whilst the rest of the field remains fairly normal. On the otherhand, too large a proportion was not chosen as the objective was to make the examination more discriminatory.

The values which were found for the younger and older age groups of normals were 2.6 and 2.0 log units respectively. These results gave a 0.6 log units difference between the two age groups at either end of the scale which indicated a decrease of 0.2 log units for each increasing 10 year age group (which follows a similar trend to the suggested filter densities). Hence the standard filter densities which have been chosen are as follows:-

Age (Years)	Filter Density (log units)
<40	2.6
40-49	2.4
50 - 59	2.2
60 - 69	2.0
70 and over	1.8

Working threshold (log units)	Range of filter densities to perceive all of the stimuli	Number of Subjects to observe 1/3rd or more stimulus points at initial filter density
2.6	2.6 - 2.2	4
2.4	2.4 - 2.2	6

Table 2 Filter densities for the 20-29 age group

Working threshold (log units)	Range of filter densities to perceive all of the stimuli	Number of Subjects to observe 1/3rd or more stimulus points at initital filter density
2.2	2.4 - 2.0	1
2.0	2.2 - 1.4	6
1.8	2.0 - 1.4	3

Table 3 Filter densities for the 60-69 age group

If a subject is unable to detect at least one third of the stimuli from 4 randomly-selected central positions and 4 peripheral positions, then the ~~working threshold~~ filter density is reduced by 0.2 log units.

It is to be noted that in this test, a high threshold value indicates a high filter density and hence improved sensitivity.

APPENDIX 3

A study on 10 Caucasians and 10 age-and sex-matched coloured subjects

The electrophysiological and psychophysical results of 10 light-eyed Caucasians ($\bar{x}$=29.2 ± 7.7yr) and 10 dark-eyed coloured persons ($\bar{x}$=29.1 ± 7.5yr; consisting of 7 Asians, 2 Africans and 1 West Indian) have been analysed by two-way analysis of variance (ANOVA) for related samples. An example of the format used for analysing the data is shown in Table 4 for the peak latency of the photopic B wave. Variance ratios (F values) have been calculated between:

1) first treatment levels, that is, a comparison of the data between right and left eyes
2) second treatment levels, that is, a comparison of the data between Caucasian and coloured subjects

and 3) the variance ratio of interactions between the two treatment levels is also calculated.

For each variance ratio, the degrees of freedom for the numerator and denominator are stated respectively from which the level of significance can be found in the table of "the critical values of F".

The macular thresholds to white and coloured lights and the visual field scores for white stimulation have been analysed by the Wilcoxon test for discrete values. An example of the presentation of data for this test is shown in Table 5 from which the "non-zero" and "T" values are calculated and the level of significance can be obtained.

SUBJECT 1

	CAU	COL
PE	36	42.5
LE	35.5	42.75

SUBJECT 2

	CAU	COL
PE	41.5	44
LE	41	44

SUBJECT 3

	CAU	COL
PE	38	42.5
LE	38	42

SUBJECT 4

	CAU	COL
PE	41.5	38.25
LE	40.5	38.75

SUBJECT 5

	CAU	COL
PE	40	42.5
LE	40	42

SUBJECT 6

	CAU	COL
PE	38.25	41
LE	38.75	40.5

SUBJECT 7

	CAU	COL
PE	39	37.5
LE	39	37

SUBJECT 8

	CAU	COL
PE	38.75	38
LE	39.75	37.5

SUBJECT 9

	CAU	COL
PE	41.25	43.25
LE	42.5	43.5

SUBJECT 10

	CAU	COL
PE	38	36.5
LE	38.5	36.5

AVERAGES

	CAU	COL	
PE	39.225	40.6	39.9125
LE	39.35	40.45	39.9
	39.2875	40.525	39.9063

VARIANCE RATIO BETWEEN FIRST TREATMENT LEVELS = .0138607
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 9

VARIANCE RATIO BETWEEN SECOND TREATMENT LEVELS = 1.62962
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 9

VARIANCE RATIO OF INTERACTIONS BETWEEN TREATMENTS = .900767
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 9

Table 4

Illustrating an example of the format used in two-way ANOVA for the photopic B wave latency in Caucasian and coloured subjects.

Subject No.	Right Eye		Left Eye	
	MT Cau	MT col	MT Cau	MT col
1	2.0	2.0	1.8	2.0
2	1.8	1.8	1.8	1.8
3	2.2	2.0	2.2	2.0
4	2.2	2.0	2.2	2.2
5	2.0	2.0	2.0	2.0
6	2.2	2.2	2.0	2.2
7	1.8	2.0	1.8	1.8
8	2.0	1.8	1.8	1.8
9	2.0	1.8	2.0	1.8
10	1.8	1.6	1.8	1.4
Non Zero value (n)	6		5	
T Value	4		5	
Significance Level	NS		NS	

For interocular differences, the macular threshold values for the right and left eyes of the Caucasians have been compared, which are as follows:-

Non Zero Value (n) 3

T Value 0

Significance Level Unspecified

Table 5 Showing the format of the data of the red macular thresholds for each eye in 10 Caucasians and 10 coloured subjects which has been analysed by the Wilcoxon test for discrete values.

In Table 5 , the log values for the right eye for the Caucasians and coloured subjects have been compared; this is repeated for the left eye. In order to test if there are any interocular differences, then the values for the right and left eyes of the Caucasians are compared for say the red macular thresholds and subsequently, this is repeated for the data of the coloured subjects (Table 5).

As the Wilcoxon test used in this study is designed for discrete values (for example, the log unit values on the Friedmann VFA), no means or standard deviations are stated in the results of this test. However, means and standard deviations of the macular thresholds and visual field scores have been given in Table 13 , as it provides an indication of the change in values for the two subject groups.

Electrophysiological Results

On looking at the results for the dark-adapted and photopic ERGs for the two subject groups (Table 6), it is seen that there are no significant differences for any of the components measured.

Similar results have been obtained for the various types of VER stimulation which have been used. (Tables 7-12).

Psychophysical Results

The results for the macular thresholds for white and coloured lights and the visual field scores are shown in Table 13 . On inspecting this table, it is seen that there is no significant difference between Caucasians and coloured subjects for the macular thresholds to green

Subject Group	A (ms) R	A (ms) L	B (ms) R	B (ms) L	AB (uV) R	AB (uV) L	A (ms) R	A (ms) L	B (ms) R	B (ms) L	OP1 (ms) R	OP1 (ms) L	OP2 (ms) R	OP2 (ms) L	AB (uV) R	AB (uV) L
1	25.15±1.15	25.03±1.30	47.38±2.18/	47.43±2.21	280.87±53.76/	271.24±43.04	19.55±1.03/	19.58±0.96	39.23±1.82/	39.35±1.90	24.20±1.10/	24.10±1.25	31.10±1.10/	31.03±1.10	102.86±25.92	105.61±29.06
2	25.58±1.70	25.68±1.66	47.79±2.49	48.3±2.64	246.48±52.59/	249.20±46.78	19.23±0.77	19.28±0.87	40.6±2.75	40.45±2.81	24.03±1.36	24.13±1.14	30.43±1.23	31.13±1.44	96.54±39.32	101.20±41.41
F value for eyes	6.57×10^{-3}		1.84		1.24		0.04		0.01		4.12×10^{-4}		4.49		2.17	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F value for groups	1.56		1.37		1.88		0.52		1.63		0.02		0.24		0.12	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F value for Interaction	0.46		1.45		2.99		5.74×10^{-3}		0.90		0.28		19.26		0.19	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS	1,9	NS

Key: 1 : Caucasians 2 : Coloured Subjects.

TABLE 6 Giving the means ± 1SD for the components of the dark-adapted and photopic ERGs in 10 Caucasians and 10 coloured subjects.

Subject Group	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L
1	123.18±6.86 / 124.03±7.12		5.77±2.88 / 5.59±1.75	
2	125.15±7.29 / 124.58±6.90		6.85±3.63 / 6.51±2.94	
F Value for Eyes DF	0.04 1,9	NS	4.55×10^{-3} 1,9	NS
F Value for Groups DF	0.20 1,9	NS	0.65 1,9	NS
F Value for Interaction DF	0.94 1,9	NS	0.59 1,9	NS

TABLE 7 Giving means ± 1 SD for the P_2 component and N_2P_2 configuration for flash stimulation in 10 Caucasians and 10 coloured subjects.

Subject Group	P_2 (ms) R	L	N_2P_2 (ms) R	L	P_2 (ms) R	L	N_2P_2 (uV) R	L
1	104.75±4.76/106.88±5.45		4.44±1.26/4.42±1.42		106.63±4.13/105.78±6.56		3.75±1.63/3.84±1.83	
2	101.88±3.70/101.93±3.90		5.82±2.26/5.65±1.89		103.23±4.50/103.75±4.66		3.53±0.77/3.95±1.48	
F Value for Eyes	2.21		2.94		0.03		2.63	
DF	1.9	NS	1.9	NS	1.9	NS	1.9	NS
F Value for Groups	2.61		4.28		1.26		5.46×10^{-3}	
DF	1.9	NS	1.9	NS	1.9	NS	1.9	NS
F Value for Interaction	3.75		2.88		0.99		1.04	
DF	1.9	NS	1.9	NS	1.9	NS	1.9	NS

TABLE 8 Giving the means ± 1SD for the P_2 component and N_2P_2 configuration for pattern reversal black/white stimulation (56' and 14') in 10 Caucasians and 10 coloured subjects.

Subject Group	P_2 (ms) R	L	N_2P_2 (uV) R	L	P_2 (ms) R	L	N_2P_2 (uV) R	L
1	109.03±5.94/109.4±5.36		3.68±5.36/3.65±1.31		110.90±5.59/109.8±5.41		3.67±0.91/3.84±0.78	
2	108.23±5.08/108.05±4.74		4.75±2.95/5.08±2.97		107.15±4.58/106.75±5.56		3.78±1.78/3.33±1.43	
F Value for Eyes DF	0.02 1,9	NS	0.99 1,9	NS	0.57 1,9	NS	0.22 1,9	NS
F Value for Groups DF	0.22 1,9	NS	2.55 1,9	NS	4.89 1,9	NS	0.11 1,9	NS
F.Value for Interaction DF	0.10 1,9	NS	0.83 1,9	NS	0.20 1,9	NS	2.22 1,9	NS

TABLE 9 Giving the means ± 1SD for the P_2 component and N_2P_2 configuration for pattern reversal red/green stimulation (56' and 14') in 10 Caucasians and 10 coloured subjects.

Subject Group	P_2(ms) R	L	N_2P_2(uV) R	L	CII(ms) R	L	CICII(uV) R	L
1	108.2±8.77/107.98±8.76		3.32±0.7/3.15±0.55		140.1±8.93/139.65±11.21		5.36±1.70/4.68±1.65	
2	107.15±7.19/107.68±7.68		4.05±2.14/4.04±2.13		139.73±12.25/104.5±13.99		6.28±3.6/6.37±3.50	
F Value for Eyes	0.05		0.29		0.03		1.08	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Groups	0.03		1.27		1.90×10^{-3}		0.99	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	0.35		0.26		0.39		1.74	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 10 Giving the means ± 1SD for the P_2 and CII components and N_2P_2 and CI CII configuration for pattern reversal and pattern onset-offset blue/yellow (56') stimulation respectively in 10 Caucasians and 10 coloured subjects.

Subject Group	CII(ms) R	CII(ms) L	CI CII(uV) R	CI CII(uV) L	CII (ms) R	CII (ms) L	CI CII (uV) R	CI CII (uV) L
1	111.45±11.98/111±13.02		4.35±1.86/3.96±1.19		115.65±11.84/114.75±12.04		4.10±1.42/4.18±1.16	
2	108.68±10.43/109.78±9.23		5.80±4.93/6.07±5.12		121.18±7.32/119.08±7.58		6.56±4.84/6.67±4.90	
F Value for Eyes DF	0.08 1,9	NS	0.09 1,9	NS	4.55 1,9	NS	0.19 1,9	NS
F Value for Groups DF	0.12 1,9	NS	2.47 1,9	NS	0.80 1,9	NS	3.23 1,9	NS
F Value for Interaction DF	1.84 1,9	NS	1.73 1,9	NS	0.70 1,9	NS	0.02 1,9	NS

TABLE 11 Giving means ± 1 SD for the CII component and CI CII configuration for pattern reversal onset-offset, black/white stimulation (56' and 14') in 10 Caucasians and 10 coloured subjects.

Subject Group	CII (ms) R	CII (ms) L	CI CII (uV) R	CI CII (uV) L	CI (ms) R	CI (ms) L	CI CII (uV) R	CI CII (uV) L
1	123.63±10.39	123.5±9.51	5.36±1.70	4.68±1.65	131.20±10.15	132±8.55	4.07±2.11	4.39±2.33
2	126.03±14.52	127.63±12.61	6.75±2.06	6.36±2.36	129.73±14.03	129.95±14.69	4.99±2.92	4.69±2.31
F Value for Eyes	1.75		1.85		0.53		1.70×10^{-3}	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Groups	0.32		1.02		0.01		0.33	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	1.06		0.10		0.06		4.08	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 12 Giving the means ±1SD for the CII component and CI CII configuration for pattern onset-offset red/green stimulation (56' and 14') in 10 Caucasians and 10 coloured subjects.

Subject Group	MACULAR THRESHOLD (log units)								Visual Field Score (log units)	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L	R	L
1	2.72±0.10/2.70±0.14 (2.6-2.8)(2.4-2.8)		2.50±0.17/2.50±0.19 (2.2-2.8)(2.2-2.8)		2.00±0.16/1.94±0.16 (1.8-2.2)(1.8-2.2)		1.00±0.13/1.04±0.16 (0.8-1.2)(0.8-1.2)		234.23±9.23/234.2±10.28	
2	2.64±0.21/2.64±0.21 (2.4-2.8)(2.4-2.8)		2.42±0.22/2.44±0.16 (2.0-2.6)(2.0-2.6)		1.92±0.17/1.90±0.24 (1.6-2.2)(1.4-2.2)		0.92±0.17/0.89±0.15 (0.6-1.2)(0.16-1.2)		233.70±11.01/234.58±11.34	
Non zero Value (n)	3	5	6	7	6	5	3	5	10	10
T Value for R & L eyes Between Groups	3	4.5	1.5	7	4	5	0	0	2.3	2.25
	Unspecified	NS	NS	NS	NS	NS	Unspecified	NS	NS	NS
Non zero Value (n)	No differences		2		3		2		9	
T Value for interocular differences for group	NS		1		0		0		22	
			Unspecified		Unspecified		Unspecified		NS	

Key: 1: Caucasian 2: Coloured Subjects.
Subject Group

TABLE 13 Giving (the means ± 1SD) and the ranges for the macular thresholds and the means ± 1SD for the visual field scores for 10 Caucasian and 10 coloured subjects.

and red and white stimulation and for the visual field scores. Unfortunately, for the other "non-zero (n)" and "T" values obtained, no decision was possible at the 5% and 1% levels of significance, that is, the table for the critical values of "T", did not specify any "non-zero" or "T" values for the results obtained.

The log sensitivities of the flicker fusion thresholds have not revealed any significant differences between the two subject groups (Table 14). However, at the highest flicker frequency tested (30Hz), it can be seen that the interocular difference and the difference between the two subject groups nearly attained significance. Generally, the standard deviations at this frequency are higher than those for the lower frequencies (Table 14), reflecting the greater difficulty experienced by subjects in discerning the flicker effect at 30Hz. It was also noted that 3 Asian subjects (who were English-speaking) were somewhat hesitant in making a decision at this frequency which could account for the results nearly reaching significance.

LOG SENSITIVITY (log units)

Subject Group	3Hz R	3Hz L	10Hz R	10Hz L	30Hz R	30Hz L
1	1.7373±0.0926/1.7459±0.1041		1.8759±0.0617/1.9281±0.0919		1.2354±0.2184/1.2087±0.2053	
2	1.7214±0.1096/1.6889±0.1051		1.8090±0.1008/1.8110±0.1127		1.0721±0.0944/1.0791±0.0931	
F Value for Eyes	4.42		1.87		5.01	
DF	1,9	NS	1,9	NS	1,9	NS
F Value for Groups	0.69		1.48		5.11	
DF	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	2.99		2.21		6.40	
DF	1,9	NS	1,9	NS	1,9	p<0.05

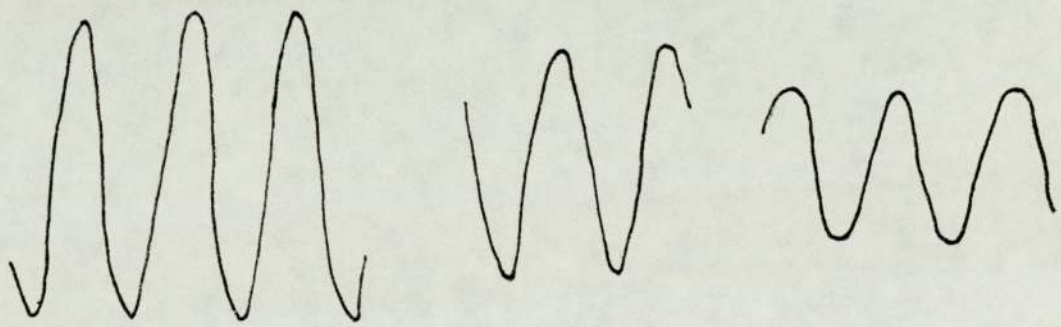
Key: 1: Caucasians 2: Coloured Subjects

TABLE 14 Giving the means ± 1SD for the log sensitivities of the flicker fusion thresholds for 10 Caucasians and 10 coloured subjects.

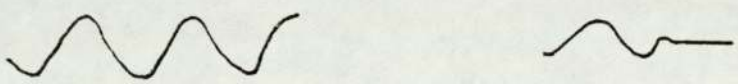
APPENDIX 4

Calibration of the Apparatus used for measuring the depth of modulation of a 2^{o} flickering source

The percentage depth of modulation of the 2^{o} flickering spot was calculated at ten successive intervals of the arbitrary scale, ranging from the minimum to maximum dial positions (0 - 1000). In order to do this, the sinusoidal waveform was obtained at each setting by placing a photocell over the flickering spot which was connected to the computer averager (Datalab DL4000B) and hence the X-Y plotter. Only one sweep was required to obtain the sinusoidal waveform at each setting (Figure 1)



Scale value	1000	800	500
M(%)	30.95	23.46	14.12



Scale value	200	100	0
M(%)	6.54	2.53	0

Figure 1

Diagram showing the traces of the sinusoidal waveforms at 6 arbitrary values of the flicker modulation scale. The numbers stated in percentages represent the depth of modulation (M).

By positioning the photocell over a 2^{o} aperture encircled by black cardboard on the surround of the apparatus and using neutral density filters over the aperture, traces of the relative amplitudes (in mm.) were acquired for the neutral density filters used (0.1, 0.2, 0.3, 0.4). The photocell was then replaced by a photometer so as to obtain the luminance of the aperture when each neutral density filter was used. The amplitude of these results were plotted against the luminance values. Since the plot was linear, it was valid to use this plot to convert the amplitudes of the sinusoidal waveforms (in mm.) to luminance (cd/m^2).

On converting the amplitudes of the sinusoidal traces at each modulation setting to the absolute light units then the depth of modulation was calculated by employing the following equation:

$$\frac{L\ max\ -\ L\ min}{L\ max\ +\ L\ min}$$

A graph was then plotted of the percentage modulation versus the arbitrary scale value, when a linear correlation was obtained (Figure 2). The equation for this graph was calculated as being,

$$Y = 0.00029x^{(m)}$$

whereby:-

Y = modulation

x = arbitrary scale value

m = a constant

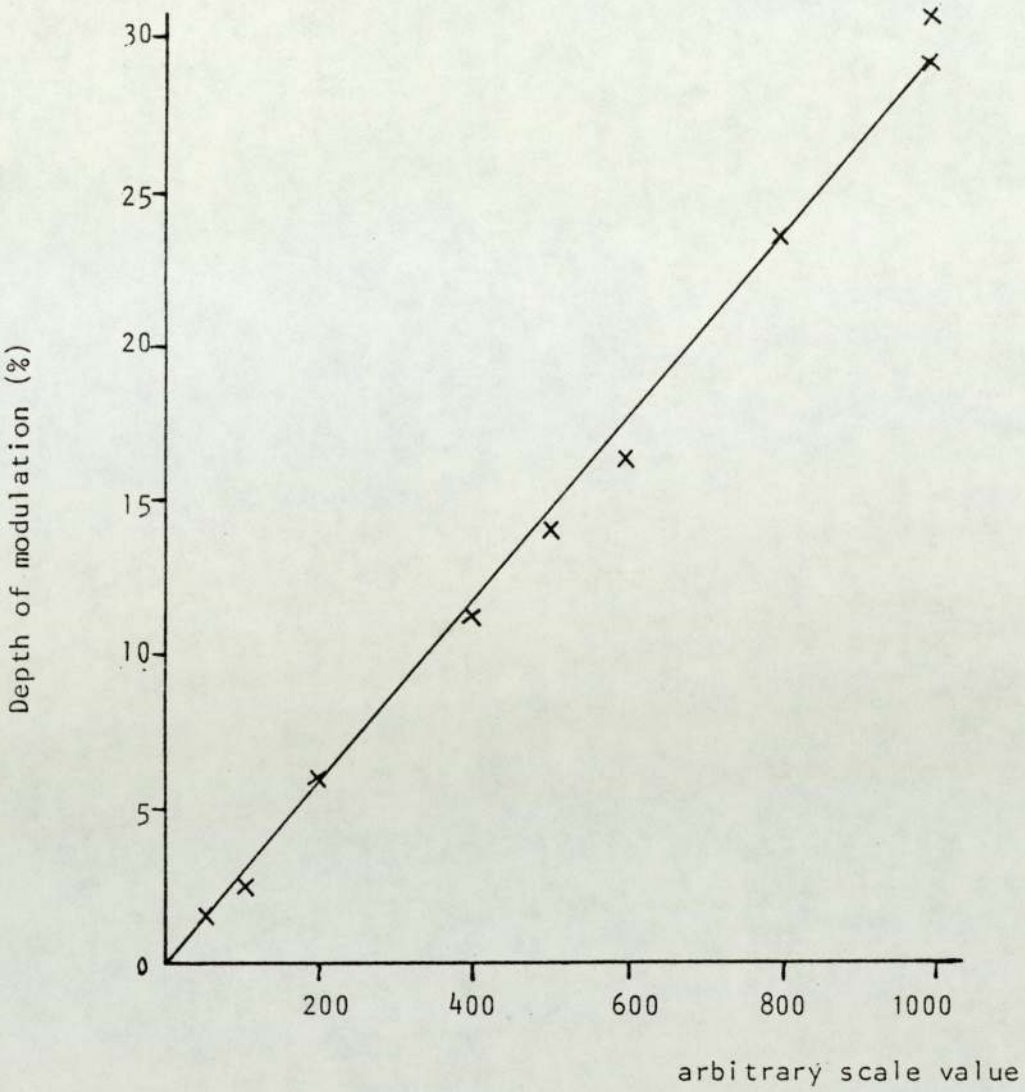


Figure 2

Graph showing the relationship between the depth of modulation and the arbitrary scale values of the flicker apparatus

The reciprocal of the 'mx' value was taken as the sensitivity of the modulation threshold value which, in turn, was converted to the logarithmic sensitivity, that is,

$$\text{log sensitivity} = \log \frac{1}{0.00029x}$$

Study on normal subjects using the flicker apparatus

The flicker fusion thresholds of the right eyes of 10 clinically normal subjects ($\bar{x}$ = 25.9 ± 3.1yr ; 4 males, 6 females) were obtained at seven frequencies.* These frequencies ranged from the low to high frequency regions whereby each succeeding frequency superceded the preceding frequency by approximately $\sqrt{3}$. This was done in order to examine the normal subjects at frequencies which ascended by a constant value and also, to make these frequencies fall in between the frequencies at which the patients were tested in a gradual progression. The patients were tested at three frequencies, that is, 3, 10 and 30Hz, which are each about three times the preceding frequency.

The flicker fusion thresholds which were obtained on the normal subjects were converted to log sensitivity values by employing the equation which was previously quoted. The mean flicker fusion log sensitivity values and the respective standard deviations at each frequency are given in Figure 3 . It can be seen that the curve assumes the characteristic shape as reported by other workers (Breukink and Doesschate, 1963; Kelly, 1964; Van der Tweel and Estevez, 1974) with a maximum sensitivity occurring at approximately 10Hz. At low frequencies, the sensitivity declines but to a lesser extent than that seen for the high frequencies.

* Frequencies of 1,2,3,10,17,30Hz. were used for the 10 normal subjects tested.

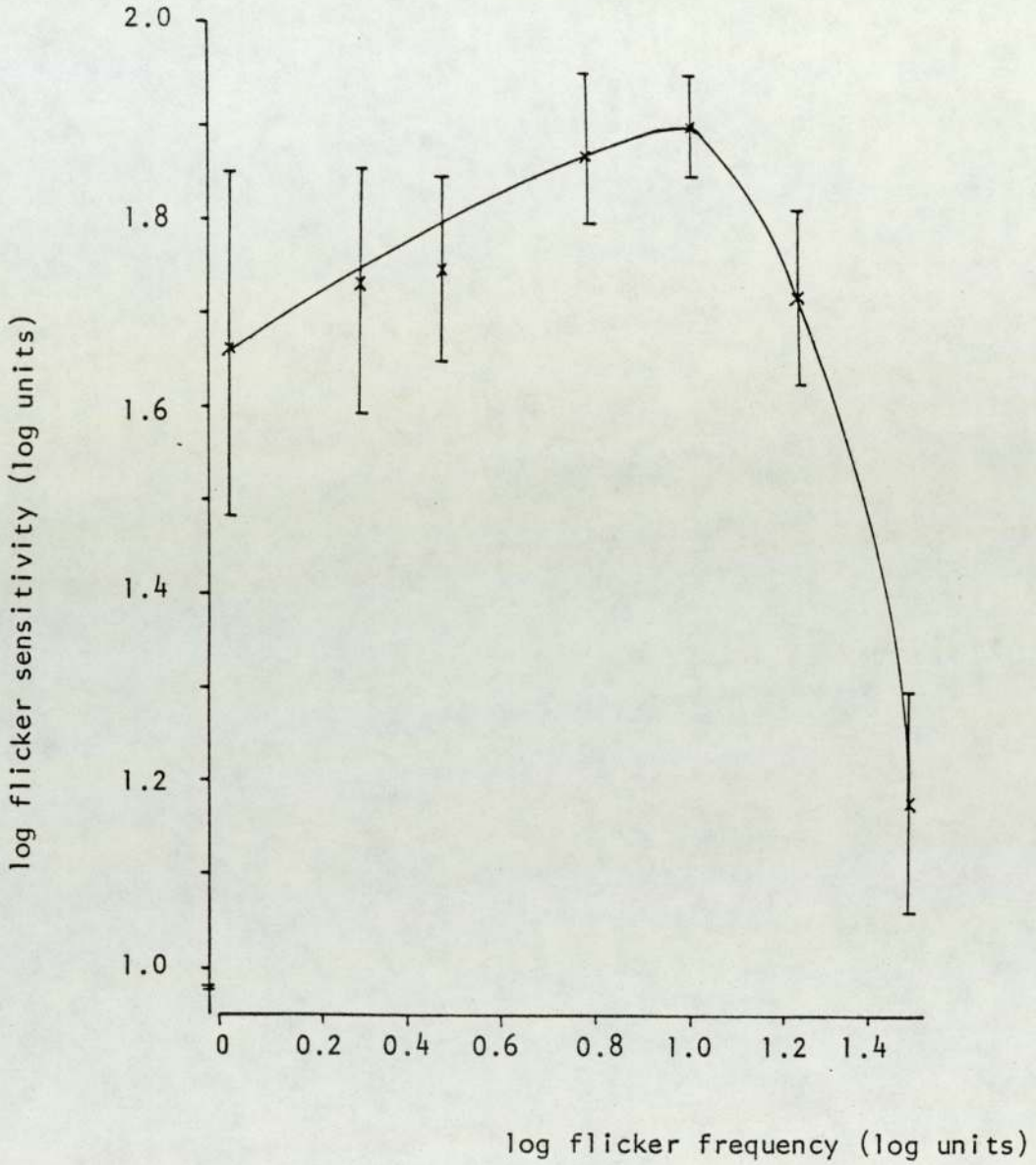


Figure 3

Graph showing the means ± 1SD for log sensitivity of the flicker fusion thresholds at seven different frequencies in 10 normal subjects

APPENDIX 5

An appendix of tables illustrating the various formats of data used for statistical analysis by ANOVA

20	30	40	50	60
246.7	254.5	200	240	225
273.4	230	293	238.3	255
253.6	260	295	240	163.3
313	205	256.5	202.6	245.5
353	230	245.7	258.3	200
313	235	278	290.4	212
300	243.3	267.8	257.5	250
300	366.7	200	182.3	225
200	200	173.6	240	238
266.7	285	203.3	236.7	265

20	30	40	50	60	
281.94	250.95	241.29	238.61	227.88	248.134

VARIANCE RATIO = 2.70368
DEGREES OF FREEDOM OF NUMERATOR = 4
DEGREES OF FREEDOM OF DENOMINATOR = 45

Table 16

Illustrating an example of the format used in one-way ANOVA for unrelated samples, using the data of the amplitude of the AB configuration for progressive age groups.

20

PR56	PR14
113.75	106.25
103.5	100
103.75	113.5
97.5	105
107.5	110
105	101.25
101.25	103.75
105	102.5
106.5	101.5
98	103

30

PR56	PR14
112	110.5
102.75	107.5
108	108
109.5	112
116.25	102.5
103.5	101
93.75	105
102.5	97.5
97.5	109
97	106

40

PR56	PR14
100	98.5
101.5	107
105	106.25
96	98
106.25	110
105	103.75
105	106.25
102	101
96	102.5
101	102.5

50

PR56	PR14
101	98.75
93.75	98.75
105	112.5
96	107
102.5	120
107.5	120
106.25	107.5
108	104.5
96	102.5
104.75	109.75

60

PR56	PR14
118.75	115
116	109.5
106.25	106.25
95	103.75
108.5	102.5
103.75	109.5
117.5	110.75
107	123.75
95	102
101.25	112.5

70

PR56	PR14
109.5	116
102	103.75
113.75	124.25
101.25	115
110	116.25
118.75	126.25
115	125
115	116.75
103	110
105.75	112.5

AVERAGES — TREATMENTS

		PR56	PR14
20	G	104.175	104.675
30	R	104.775	105.9
40	O	101.775	103.575
50	U	102.075	108.125
60	P	108.9	109.55
70	S	109.4	116.575
		104.85	108.067

VARIANCE RATIO BETWEEN GROUPS = 5.13878
DEGREES OF FREEDOM = 5 , 54

VARIANCE RATIO BETWEEN TREATMENTS = 16.7577
DEGREES OF FREEDOM = 1 , 54

INTERACTION VARIANCE RATIO = 2.03857
DEGREES OF FREEDOM = 5 , 54

Table 17

Illustrating an example of the format used in two-way ANOVA for unrelated samples, using the data of the P_2 latency for pattern reversal 56' and 14' stimulation for progressive age groups.

20

3HZ	10HZ	30HZ
1.6773	1.9694	.9593
1.6597	1.8519	1.103
1.6238	1.8474	1.2113
1.7096	1.9041	1.3389
1.8052	1.928	1.1675
1.873	1.8199	.9727
1.9334	1.8844	1.2532
1.8961	1.8892	1.2086
1.6925	1.7668	1.0304
1.6614	1.8317	1.01

30

3HZ	10HZ	30HZ
1.7247	1.9499	1.0874
1.707	1.9062	1.1948
1.72	1.815	1.3783
1.7007	1.9935	1.1716
1.5691	1.6684	1.0526
1.6614	1.8317	1.01
1.7096	1.9269	1.1205
1.7064	1.8474	1.1081
1.5891	1.758	.9592
1.6222	1.815	1.0257

40

3HZ	10HZ	30HZ
1.6894	1.7348	.9377
1.6655	1.8991	.8329
1.4923	1.6031	.8748
1.6539	1.843	1.242
1.728	1.8806	1.1362
1.6851	1.7362	.8753
1.7234	1.7833	.7669
1.7933	1.9302	1.152
1.6031	1.8216	1.2681
1.7846	1.7064	.9486

50

3HZ	10HZ	30HZ
1.7181	1.83	1.302
1.7544	1.8275	.8662
1.6743	1.6988	1.1638
1.6522	1.8796	1.2338
1.7616	1.7856	.9292
1.7609	1.8283	.8708
1.6108	1.7438	.6454
1.5941	1.6175	.7172
1.769	1.8199	.7972
1.7757	1.8582	.9021

60

3HZ	10HZ	30HZ
1.4731	1.629	.5938
1.5668	1.6455	.6054
1.6212	1.8519	.9849
1.6876	1.7247	.7216
1.6988	1.9144	.946
1.7369	1.7949	.6631
1.6925	1.6483	.7019
1.6383	1.6441	.7972
1.5668	1.6455	.6054
1.581	1.7032	.87702

70

3HZ	10HZ	30HZ
1.6418	1.7137	.6725
1.4331	1.6962	.7596
1.4263	1.5131	.7355
1.4237	1.4459	.7689
1.6056	1.7348	.9399
1.6389	1.5868	.7367
1.7038	1.7879	.6679
1.6041	1.7096	.6101
1.495	1.5819	.6073
1.7181	1.7972	.6654

AVERAGES

TREATMENTS

GROUPS	3HZ	10HZ	30HZ
20	1.7532	1:86928	1.12549
30	1.67102	1.8512	1.11082
40	1.67986	1.79383	1.00345
50	1.70711	1.78892	.94277
60	1.6263	1.72015	.749632
70	1.56904	1.65671	.71638
	1.66776	1.78001	.941424

VARIANCE RATIO BETWEEN GROUPS = 15.1011
DEGREES OF FREEDOM = 5 , 54

VARIANCE RATIO BETWEEN TREATMENTS = 1292.22
DEGREES OF FREEDOM = 2 , 108

INTERACTION VARIANCE RATIO = 4.67994
DEGREES OF FREEDOM = 10 , 108

Table 18

Illustrating the format used for analysing the log sensitivity data of the flicker fusion thresholds at three frequencies for progressive age groups. Note, that in addition to the significant variance ratios for the groups and treatments, there is also a significant interaction variance ratio.

SUBJECT 1

	VIS1	VIS2	VIS3
RE	121.75	120	118.5
LE	123.75	120	118.5

SUBJECT 2

	VIS1	VIS2	VIS3
RE	127.5	127.5	135
LE	126.25	127.5	127.5

SUBJECT 3

	VIS1	VIS2	VIS3
RE	120.75	130	125
LE	119.5	130	122.5

SUBJECT 4

	VIS1	VIS2	VIS3
RE	127.5	148	136.25
LE	126	145.5	135

SUBJECT 5

	VIS1	VIS2	VIS3
RE	131.5	129	125.5
LE	133	127.5	133

SUBJECT 6

	VIS1	VIS2	VIS3
RE	131.5	152.5	141.1
LE	127.5	148.75	145.5

SUBJECT 7

	VIS1	VIS2	VIS3
RE	125	125	127.5
LE	127.5	135	130

SUBJECT 8

	VIS1	VIS2	VIS3
RE	127.5	134	131.75
LE	130.5	134	133

SUBJECT 9

	VIS1	VIS2	VIS3
RE	124.25	126.25	132.5
LE	124.25	125	131.25

SUBJECT 10

	VIS1	VIS2	VIS3
RE	133.25	133.5	134.5
LE	135.5	128.5	132

SUBJECT 11

	VIS1	VIS2	VIS3
RE	120.5	126.5	125
LE	118.25	122.5	122.5

SUBJECT 12

	VIS1	VIS2	VIS3
RE	131	164.5	150
LE	128.5	140.2	141.75

SUBJECT 13

	VIS1	VIS2	VIS3
RE	135.25	135	128
LE	131.25	136.25	133

SUBJECT 14

	VIS1	VIS2	VIS3
RE	135.75	135	135
LE	138	142.5	135

SUBJECT 15

	VIS1	VIS2	VIS3
RE	139	140	145
LE	142	145	145

AVERAGES

	VIS1	VIS2	VIS3	
RE	128.8	135.117	132.707	132.208
LE	128.783	133.88	132.367	131.677
	128.792	134.498	132.537	131.942

VARIANCE RATIO BETWEEN FIRST TREATMENT LEVELS = .280944
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 14

VARIANCE RATIO BETWEEN SECOND TREATMENT LEVELS = 5.57209
DEGREES OF FREEDOM OF NUMERATOR = 2
DEGREES OF FREEDOM OF DENOMINATOR = 28

VARIANCE RATIO OF INTERACTIONS BETWEEN TREATMENTS = .31953
DEGREES OF FREEDOM OF NUMERATOR = 2
DEGREES OF FREEDOM OF DENOMINATOR = 28

Table 19

Illustrating an example of the format used in two-way ANOVA for related samples, using the data of the P_2 latency to flash stimulation in the visually unaffected tuberculotic patients, investigated on three occasions.

APPENDIX 6

Study on the data of each occipital hemisphere of each eye for the various forms of VER stimulation (performed on the data of the 20-29 age group)

The data for each occipital hemisphere, that is O_2 and O_1, of each eye has been analysed for the various forms of VER stimulation used in this project. An example of the format of the data for analysis by two-way ANOVA is given in Figure 4 and the levels of significance for each type of VER stimulation are shown in Tables 20-23

It can be seen from Tables 20-23 that there is no significant difference between the right and left hemispheres of each eye for any form of VER stimulation and in addition to this, there is no marked difference between the right hemisphere for the right and left eyes (similar results have been observed for the left hemisphere). For this reason, it has been decided to use the mean of the right and left hemispheres for each eye in the analysis of the results for both peak latencies and amplitudes.

SUBJECT 1

	RH	LH
RE	137.5	132.5
LE	137.5	137.5

SUBJECT 2

	RH	LH
RE	132.5	135
LE	132.5	130

SUBJECT 3

	RH	LH
RE	110	115
LE	110	110

SUBJECT 4

	RH	LH
RE	125	120
LE	125	122.5

SUBJECT 5

	RH	LH
RE	115	117.5
LE	115	115

SUBJECT 6

	RH	LH
RE	127.5	122.5
LE	127.5	127.5

SUBJECT 7

	RH	LH
RE	135	132.5
LE	132.5	135

SUBJECT 8

	RH	LH
RE	140	140
LE	135	140

SUBJECT 9

	RH	LH
RE	110.5	116
LE	121	118

SUBJECT 10

	RH	LH
RE	131	131
LE	134	134

AVERAGES

	RH	LH	
RE	126.4	126.2	126.3
LE	127	126.95	126.975
	126.7	126.575	126.638

VARIANCE RATIO BETWEEN FIRST TREATMENT LEVELS = .526515
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 9

VARIANCE RATIO BETWEEN SECOND TREATMENT LEVELS = .0334573
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 9

VARIANCE RATIO OF INTERACTIONS BETWEEN TREATMENTS = 8.63461E-03
DEGREES OF FREEDOM OF NUMERATOR = 1
DEGREES OF FREEDOM OF DENOMINATOR = 9

Figure 4

Illustrating the format used for analysing the hemispherical data, showing the CII latency for pattern onset-offset 14' black/white stimulation

	Flash		PR 56' B/W		PR 14' R/G		PR 56' B/Y	
	RH	LH	RH	LH	RH	LH	RH	LH
R	122.10±8.17 / 121.80±7.13		104.30±5.95 / 104.10±4.41		109.35±5.71 / 109.35±6.39		108.55±7.74 / 107.75±6.40	
L	124.60±6.66 / 122.65±8.51		105.50±6.43 / 105.75±6.24		109.35±7.27 / 108.10±6.89		108.00±7.71 / 107.00±6.85	
F Value for Eyes	2.19		1.53		0.17		0.48	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Hemispheres	1.34		1.30		1.00		0.59	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	1.34		0.06		2.14		0.04	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

Key: RH - Right Hemisphere; LH - Left Hemisphere; R - Right Eye; L - Left Eye; PR - Pattern Reversal B/W - Black/white; R/G - Red/Green; B/Y - Blue/Yellow.

Table 20 Giving the means ± 1 SD for the P_2 latency for the right and left hemispheres (O_2,O_1) of each eye for the data of the 20-29 age group.

	P O/N 56' B/W RH LH	P O/N 14' R/G RH LH	P O/N 56' B/Y RH LH
R	105.10±9.33 / 108.65±6.92	126.40±11.03 / 126.20±8.99	139.10±8.21 / 141.90±7.80
L	105.35±8.89 / 105.80±7.51	127.00±9.17/ 126.95±10.20	142.60±9.72 / 141.80±6.52
F Value for Eyes DF	4.24 1,9 NS	0.53 1,9 NS	2.92 1,9 NS
F Value for Hemispheres DF	1.77 1,9 NS	0.03 1,9 NS	1.22 1,9 NS
F Value for Interaction DF	4.02 1,9 NS	8.63×10^{-3} 1,9 NS	5.05 1,9 NS

Key: P O/N - Pattern Onset/Offset.

Table 21 Giving the means ± 1 SD for the CII latency for the right and left hemispheres (O_2,O_1) of each eye for the data of the 20-29 age group.

	Flash		PR 56' B/W		PR 14' R/G		PR 56' B/Y	
	RH	LH	RH	LH	RH	LH	RH	LH
R	5.46±2.86/4.71±2.00		5.31±1.86/5.24±1.31		3.85±1.30/3.74±1.35		3.25±0.62/2.86±0.62	
L	5.49±2.09/4.64±1.40		4.70±0.90/4.60±0.80		3.87±0.97/3.65±1.36		3.06±0.67/3.42±0.82	
F Value for Eyes	2.36×10^{-3}		1.16		7.78×10^{-3}		0.15	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Hemispheres	4.87		0.07		0.87		2.28	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	0.08		9.16×10^{-3}		0.08		0.73	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

Table 22 Giving the means ± 1 SD for the N_2P_2 configuration for the right and left hemispheres (O_2,O_1) of each eye for the data of the 20-29 age group.

	PO/N 56' B/W RH	LH	PO/N 14' R/G RH	LH	PO/N 56' B/Y RH	LH
R	3.96± 2.11/4.07±1.58		6.21±2.02/7.08±2.11		5.19±1.76/5.85±1.85	
L	3.80±1.65/ 3.68±1.35		6.18±2.13/6.92±2.09		4.48±1.98/5.36± 2.36	
F Value for Eyes DF	1.25 1,9	NS	0.14 1,9	NS	3.31 1,9	NS
F Value for Hemispheres DF	5.08×10^{-3} 1,9	NS	3.42 1,9	NS	2.03 1,9	NS
F Value for Interaction DF.	0.27 1,9	NS	0.12 1,9	NS	0.51 1,9	NS

Table 23 Giving the means ± 1 SD for the CI CII configuration for the right and left hemispheres (0_2,0_1) of each eye for the data of the 20-29 age group.

APPENDIX 7

Study on 10 repeated normal subjects

Ten visually clinically normal subjects (6 males, 4 females; $\bar{x}$ = 33.7 ± 11.0 yr) were repeated on the tests used in this project after approximately 8 weeks. The electrophysiological data and the flicker fusion log sensitivity data have been analysed by two-way ANOVA for related samples whilst the visual field data has been analysed by the Wilcoxon test.

Electrophysiological Results

On inspecting the results for the components of the dark-adapted and photopic ERGs, no significant differences have been obtained between the two investigations (Table 24, 25)

The results for the VER investigation also do not reveal any marked differences for any form of stimulation. One of the subjects who demonstrated noticeably delayed latencies for the CII component in pattern onset-offset stimulation on the first investigation, was repeated. It was found that similar results were obtained on the second investigation which would indicate that the latencies are fairly stable for given occipital electrode positions. (Table 26-31).

For the various forms of pattern onset-offset stimulation, the components have been seen on the initial and repeated traces in both eyes in the following percentages (excluding the data for the subject with noticeably delayed responses).

Dark-adapted Low Intensity

No. of Visit.	A(ms) R	A(ms) L	B(ms) R	B(ms) L	AB(uV) R	AB(uV) L
Visit 1	26.24±2.05	26.39±2.14	48.69±2.03	48.79±2.04	255.44±36.50	246.53±34.34
Visit 2	25.88±1.39	26.16±1.55	49.40±1.14	49.26±1.48	237.54±22.82	235.49±27.92
F Value For Eyes	0.53		5.09×10^{-3}		0.02	
DF	1,9	NS	1,9	NS	1,9	NS
F Value For Visits	0.41		1.15		0.59	
DF	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	0.34		0.21		1.39	
DF	1,9	NS	1,9	NS	1,9	NS

TABLE 24 Giving the means ± 1SD for the dark adapted ERG in 10 repeated normal subjects.

PHOTOPIC

No. of Visit.	A(ms) R	A(ms) L	B(ms) R	B(ms) L	OP_1(ms) R	OP_1(ms) L	OP_2(ms) R	OP_2(ms) L	AB(uV) R	AB(uV) L
Visit 1	20.3±0.86/ 20.1±0.97		40.88±1.92/ 40.68±1.97		25.28±1.43/ 25.07±1.25		31.38±1.44/ 31.83±1.35		97.56±25.06/ 104.24±33.75	
Visit 2	20.1±0.96/ 20.2±0.86		41.33±1.45/ 41.08±1.42		24.63±0.96/ 24.54±0.88		31.25±1.00/ 31.23±0.99		100.93±21.16/ 101.15±21.62	
F Value for Eyes DF	0.17 1,9	NS	2.68 1,9	NS	1.27 1,9	NS	0.86 1,9	NS	0.76 1,9	NS
F Value for Visits DF	0.07 1,9	NS	0.86 1,9	NS	2.47 1,9	NS	0.80 1,9	NS	2.95×10^{-4} 1,9	NS
F Value for Interaction DF	0.84 1,9	NS	0.23 1,9	NS	0.20 1,9	NS	6.99 1,9	NS	2.35 1,9	NS

TABLE 25 Giving the means ± 1SD for the photopic ERG in 10 repeated normal subjects.

No. of Visit.	P_2(ms) R	P_2(ms) L	N_2P_2(uV) R	N_2P_2(uV) L
Visit 1	124.43 ± 5.87 / 125.40 ± 5.43		6.53 ± 2.62 / 7.10 ± 3.47	
Visit 2	124.68 ± 5.11 / 125.73 ± 5.05		6.18 ± 2.26 / 5.93 ± 1.83	
F Value for eyes	4.76		0.21	
DF	1,9	NS	1,9	NS
F Value for Visits	0.24		0.55	
DF	1,9	NS	1,9	NS
F Value for Interaction	9.55×10^{-3}		1.20	
DF	1,9	NS	1,9	NS

TABLE 26 Giving the means ± 1 SD for the P_2 component and N_2P_2 configuration for flash stimulation in 10 repeated normal subjects.

No. of Visit.	P_2(ms)		N_2P_2(uV)		P_2(ms)		N_2P_2(uV)	
	R	L	R	L	R	L	R	L
Visit 1	104.68±6.34 / 105.25±7.50		4.91±1.50 / 4.81±2.05		104.33±3.78 / 105.18±3.52		3.53±0.89 / 3.89±1.18	
Visit 2	106.55±6.70 / 105.83±6.01		5.01±1.27 / 4.88±1.19		105.03±3.90 / 104.98±4.18		3.41±0.91 / 3.38±0.92	
F Value for Eyes	8.63×10^{-3}		0.35		0.07		1.68	
DF	1,8	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Visits	1.09		0.05		0.10		0.94	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	2.68		3.24×10^{-3}		0.31		3.86	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 27 Giving the means ± 1SD for the P_2 component and N_2P_2 configuration for pattern reversal black/white stimulation (56' and 14') in 10 repeated normal subjects.

No. of Visit	P_2(ms) R	L	N_2P_2(uV) R	L	P_2(ms) R	L	N_2P_2(uV) R	L
Visit 1	109.7±4.50 / 109.58±4.36		3.31±0.74 / 3.75±0.84		109.68±5.25 / 108.45±5.17		3.57±0.95 / 2.91±1.32	
Visit 2	109.0±3.22 / 108.9±4.34		3.34±0.59 / 3.32±0.63		107.58±5.08 / 108.13±4.87		3.62±0.60 / 3.21±0.86	
F Value for eyes	0.017		2.67		0.16		1.48	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Visits	1.20		0.73		1.86		1.95	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	2.69×10^{-4}		4.42		1.22		1.66	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 28 Giving the means ± 1SD for the P_2 component and N_2P_2 configuration for pattern reversal, red/green stimulation (56' and 14') in 10 repeated normal subjects.

No. of Visit.	P_2(ms) R	L	N_2P_2(uV) R	L	CII(ms) R	L	CI CII(uV) R	L
Visit 1	109.13±6.81 / 107.68±6.93		3.11±0.76 / 2.95±0.74		146.80±17.81/148.20±19.21		5.51±2.12 / 5.33±1.55	
Visit 2	108.03±7.18 / 102.30±7.19		3.13±0.76 / 2.92±0.57		149.0±17.40 /149.28±18.89		6.03±2.58 / 5.45±2.20	
F Value for Eyes	4.58		2.79		0.80		0.91	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Visits	0.26		1.02×10^{-3}		1.17		0.31	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	0.21		0.44		0.29		0.36	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 29 Giving the means ± 1 SD for the P_2 and CII components and N_2P_2 and CI CII configurations for pattern reversal andpattern onset-offset blue/yellow (56') stimulation respectively in 10 repeated normal subjects.

No. of Visit	CII(ms)		CI CII(uV)		CII(ms)		CI CII(uV)	
	R	L	R	L	R	L	R	L
Visit 1	112.65±20.65 / 114.08±21.06		4.53±1.22 / 4.17±1.11		127.83±24.60 / 126.90±23.01		4.43±0.60 / 4.18±1.16	
Visit 2	117.3±19.69 / 115.73±19.34		4.39±1.19 / 4.45±0.94		126.0±21.83 / 128.13±22.21		4.40±1.02 / 4.70±1.33	
F value for Eyes	6.22×10^{-3}		0.32		0.68		6.74×10^{-3}	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F value for Visits	0.97		0.054		0.016		0.52	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	3.11		1.26		3.00		1.82	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 30 Giving the means ± 1 SD for the CII component and CI CII configuration for pattern onset-offset, black/white stimulation (56' and 14') in 10 repeated normal subjects.

No. of Visit	CII (ms)		CI CII(uV)		CII (ms)		CI CII (uV)	
	R	L	R	L	R	L	R	L
Visit 1	128.53±19.00 / 129.88±20.56		4.29±1.65 / 4.40±2.00		136.58±18.49 / 137.73±18.38		5.11±1.18 / 5.43±1.31	
Visit 2	133.33±16.35 / 132.93±16.66		3.78±1.10 / 3.73±1.15		139.78±15.71 / 139.65±15.44		5.30±1.67 / 5.03±1.92	
F Value for Eyes	0.11		0.063		0.37		0.10	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Visits	2.70		3.30		0.64		0.098	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS
F Value for Interaction	1.13		0.48		0.50		4.24	
DF	1,9	NS	1,9	NS	1,9	NS	1,9	NS

TABLE 31 Giving the means ± 1SD for the CII component and CI CII configuration for pattern onset-offset, red/green stimulation (56' and 14') in 10 repeated normal subjects.

	CI	CII	CIII	off-response
56' B/W	77.8	100	66.7	55.6
14' B/W	66.7	100	44.4	33.3
56' R/G	77.8	100	33.3	55.6
14' R/G	55.6	100	44.4	55.6
56' B/Y	44.4	100	44.4	44.4

From the above data, the CII component has been the most consistent in appearance, followed by CI.

Psychophysical Results

For the macular thresholds to white, red and blue stimulation and the visual field scores, no significant differences have been observed.(Table 32) However, no decision could be made for the "non zero" and "T" values obtained. Nevertheless, on inspecting the means and standard deviations for the initial and repeat investigations, it is hardly likely that there is any marked difference.

On considering the log threshold values obtained for each stimulus point in the FVFA, it has been found that the number of points which maintain the same values on each investigation are as follows:-

	No of points with the same values (expressed as a percentage of the total no. of points)	
1	80.6%	($^{79}/_{98}$)
2	84.7%	($^{83}/_{98}$)
3	96.9%	($^{95}/_{98}$)
4	76.5%	($^{75}/_{98}$)

5	78.6%	($^{77}/_{98}$)
6	81.6%	($^{80}/_{98}$)
7	73.5%	($^{72}/_{98}$)
8	83.7%	($^{82}/_{98}$)
9	72.4%	($^{71}/_{98}$)
10	70.4%	($^{69}/_{98}$)
	$\bar{x}$ = 79.89 ±	7.68%

TABLE 33

The total number of points (for all 10 subjects) which differ on each investigation, is 197. Only 4 of these points have a difference of 0.4 log units on the initial and repeat investigations in 3 subjects, whilst the remainder differ by 0.2 log units. Of the 4 points with a 0.4 log unit difference, 3 were near the blind spot which could be explained by some fluctuation in fixation, therefore giving rise to this variation in sensitivity. It should also be mentioned that during routine testing of the visual field, there are two stimulus points on the visual field chart which lie just outside the dotted ovals for the blind spot and are often substantially reduced in sensitivity in normal subjects (that is, point M on the right half of the chart and point K on the left half - Figure 5.18). This reduction could be due to angioscotomata and therefore, it has not been considered to be abnormal in suspect patients. This has also been reported by Gutteridge (1983).

Before ending this section on the visual fields, it should be said that the fluctuations in the log threshold values on repeat investigations, did not fall beyond 0.4 log units of the testing thresholds, except for 2 values (both for point M) near the blind spot. Koerner

No. of Visit	MACULAR THRESHOLD (log units)								Visual Field Score (log units)	
	White		Green		Red		Blue			
	R	L	R	L	R	L	R	L	R	L
Visit 1	2.7±0.105/2.7±0.105 (2.6-2.8) (2.4-2.8)		2.48±0.14/2.5±0.11 (2.2-2.6) (2.4-2.8)		1.98±0.15/1.98±0.18 (1.8-2.2) (1.8-2.2)		1.02±0.20/1.02±0.20 (0.8-1.4) (0.8-1.4)		230.48±12.29/232.18±12.04	
Visit 2	2.68±0.103/2.70.141 (2.6-2.8) (2.4-2.8)		2.47±0.13/2.47±0.16 (2.2-2.6) (2.2-2.6)		2.02±0.11/2.02±0.11 (1.8-2.2) (1.8-2.2)		1.04±0.18/1.04±0.21 (0.8-1.4) (0.8-1.4)		231.98±11.81/232.32±12.59	
Non zero value(n) value for right and left eyes respect-ively on 1st & 2nd visits.	3	2	1	2	5	No difference	No difference	4	10	10
	2	1	0	0	6			4	13	22.5
	NS	Unspecified	Unspeci-fied	Unspeci-fied.	NS	NS	NS	NS	NS	NS
Non zero value (n) T value for interocular difference on 1st visit.	No difference		1		4		No difference		9	
			0		5				6	
	NS		Unspecified		Unspecified		NS		NS	

TABLE 32 Giving the (means ± 1SD) and ranges for the macular thresholds and the means ± 1 SD for the visual field scores in 10 repeated normals.

et al. (1977) and Fankhauser and Bebie (1979) reported that in order to reduce the threshold noise and variability in visual field testing, then averaging methods (for example, the method employed on the Octopus) should be used. However, it is felt that from the above results whereby the fluctuations still remained within the 0.4 log unit range from the testing threshold, then the variability should not create a marked problem.

For the log sensitivity values for the flicker fusion thresholds, no significant differences have been observed at any of the three frequencies (Table 34).

LOG SENSITIVITY (log units)

No. of Visit	3 Hz R	3 Hz L	10 Hz R	10 Hz L	30 Hz R	30 Hz L
Visit 1	1.686±0.111 / 1.6905±0.097		1.817±0.127 / 1.810±0.095		1.106±0.149 / 1.079±0.149	
Visit 2	1.709±0.093 / 1.687±0.108		1.843±0.116 / 1.836±0.106		1.070±0.095 / 1.068±0.100	
F Value for eyes DF	0.52 1,9	NS	0.42 1,9	NS	2.36 1,9	NS
F Value for Visits DF	0.10 1,9	NS	2.67 1,9	NS	1.00 1,9	NS
F Value for Interaction DF	2.34 1,9	NS	2.67×10^{-4} 1,9	NS	2.49 1,9	NS

TABLE 34 Giving the means ±1SD for the log sensitivities of the flicker fusion thresholds in 10 repeated normals.

APPENDIX 8

TABLES SHOWING INTEROCULAR RATIOS FOR THE ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL RESULTS

Age Range	FLASH			PATTERN REVERSAL - BLACK/WHITE				PATTERN REVERSAL - RED/GREEN			
	N_2(ms)	P_2(ms)	N_2P_2(uV)	P_2(ms) 56'	N_2P_2(uV) 56'	P_2(ms) 14'	N_2P_2(uV) 14'	P_2(ms) 56'	N_2P_2(uV) 56'	P_2(ms) 14'	N_2P_2(uV) 14'
20-29	0.93±0.08	0.97±0.03	0.79±0.18	0.97±0.02	0.75±0.21	0.97±0.03	0.85±0.14	0.97±0.02	0.85±0.13	0.96±0.03	0.78±0.13
60-69	0.94±0.10	0.97±0.03	0.82±0.11	0.97±0.01	0.73±0.10	0.96±0.02	0.73±0.13	0.98±0.02	0.81±0.13	0.96±0.02	0.82±0.10

Age Range	PATTERN REVERSAL BLUE/YELLOW		PATTERN ONSET-OFFSET BLUE/YELLOW		PATTERN ONSET-OFFSET - BLACK/WHITE				PATTERN ONSET-OFFSET RED/GREEN			
	P_2(ms) 56'	N_2P_2(uV) 56'	CII(ms) 56'	CI CII(ms) 56'	CII(ms) 56'	CI CII(ms) 14'	CII(ms) 14'	CI CII(uV) 14'	CII(ms) 56'	CI CII(uV) 56'	CII(ms) 14'	CI CII(uV) 14'
20-29	0.98±0.02	0.85±0.15	0.98±0.01	0.85±0.15	0.99±0.01	0.72±0.16	0.98±0.01	0.79±0.13	0.99±0.09	0.71±0.18	0.98±0.01	0.85±0.17
60-69	0.97±0.10	0.81±0.13	0.96±0.03	0.72±0.17	0.97±0.03	0.88±0.10	0.98±0.02	0.81±0.14	0.97±0.03	0.77±0.13	0.97±0.02	0.83±0.09

TABLE 35 Showing interocular ratios for latencies and amplitudes for flash, pattern reversal and pattern onset-offset stimulation in the 20-29 and 60-69 age groups.

Age Range	MACULAR THRESHOLD				Visual Field Score
	White	Green	Red	Blue	
20-29	0.992±.025	0.976±0.039	0.99±0.032	0.983±0.054	0.995 ± 0.005
60-69	0.977±0.037	0.975±0.04	0.978±0.046	0.964±0.082	0.984 ± 0.017

TABLE 36 Showing interocular ratios for macular thresholds and visual field scores in the 20-29 and 60-69 age groups.

Age Range	3Hz	10Hz	30Hz
20-29	0.975 ± 0.018	0.945 ± 0.04	0.976 ± 0.016
60-69	0.979 ± 0.012	0.965 ± 0.039	0.952 ± 0.03

TABLE 37 Showing interocular ratios for the log sensitivities of the flicker fusion thresholds in the 20-29 and 60-69 age groups.

APPENDIX 9

Calibration of the colour checkerboard transparencies

1 Red/Green transparency

The spectral absorptance curves were obtained for each of two red and two green squares in the central region of the red/green checkerboard transparency by using an Anaspec microspectrophotometer. From the graph of absorbance versus wavelength for the equienergy spectrum, the mean absorptance values were noted for 13 different wavelengths (430-690nm). The absorptance data (A) was converted to transmittance (T) by employing the following equation:

$$T = {}^{1}/_{A}$$

This transmittance data was then used to obtain tristimulus values X, Y, Z*, by weighting it with the CIE colour matching functions $\bar{x}(\lambda)$, $\bar{y}(\lambda)$ and $\bar{z}(\lambda)$ (Wyszecki and Stiles 1967). A correction factor (cf) was also applied for the spectral emissivity of the tungsten halogen projector lamp used to illuminate the transparencies (Table 38). On summing the values of the X column, and hence the Y and Z columns for the red and green squares respectively, the summed tristimulus values for each square were obtained (Table 39). For the red square, it can be seen that the maximum sum has been obtained for the X value followed by Y and then Z. For the green square, the maximum sum has been obtained for the Y value, followed by X and then Z (Table 39).

* The transformation of the trichromatic system based on the primaries R, G and B to one based on new primaries X, Y and Z ensures that the tristimulus values of any real colour are never negative.

(nm)	A	T	X($\bar{x}$Tcf)	Y($\bar{y}$Tcf)	Z($\bar{z}$Tcf)
430	1.8472	0.541	0.029	0.001	0.143
450	1.9657	0.509	0.044	0.005	0.230
470	1.8688	0.535	0.031	0.015	0.207
490	1.5563	0.643	0.007	0.047	0.106
510	1.3300	0.752	0.003	0.161	0.051
530	1.3407	0.746	0.062	0.322	0.016
550	1.3946	0.717	0.175	0.402	0.004
570	1.2653	0.790	0.372	0.465	0.001
590	0.8666	1.154	0.808	0.596	0.000
610	0.5325	1.878	1.369	0.687	0.000
630	0.3817	2.620	1.331	0.549	0.000
650	0.3170	3.155	0.748	0.282	0.000
690	0.2524	3.962	0.083	0.030	0.000
			5.062	3.562	0.758

Table 38 showing the mean absorptance and transmittance data and the tristimulus values at 13 different wavelengths for the red squares

Red square	Summed X value	Summed Y value	Summed Z value	Chromaticity co-ordinate for peak x	Chromaticity co-ordinate for peak y
Red	5.062	3.562	0.758	0.6659	0.3341
Green	3.588	4.345	0.985	0.3016	0.6922
Blue	3.818	5.266	4.434	not given as peak is distorted	
Yellow	7.407	6.686	1.302	0.4441	0.5546

Table 39 showing the summed tristimulus values and chromaticity co-ordinates (of the peak wavelengths) for the coloured squares

2 Blue/Yellow transparency

The above procedure was repeated for the blue and yellow squares and the respective X, Y and Z summed tristimulus values are shown in Table 39.

As the coloured checkerboard transparencies were viewed under photopic conditions, this was taken into account my multiplying the transmittance data at the 13 representative wavelengths by the photopic standard relative luminous efficiency function. This enabled a graph of relative luminous efficiency versus wavelength to be plotted for the red, green, blue and yellow squares whereby peaks are seen at 610, 550 and 575nm respectively (Figure 5a and 5b). On inspecting Figure 5b, it is observed that the peak for the blue curve has been shifted over to 550nm. This is due to the low values for the photopic luminous efficiency function within the blue region of the spectrum however, in spite of this, on viewing the transparency there was a strong sensation of blue.

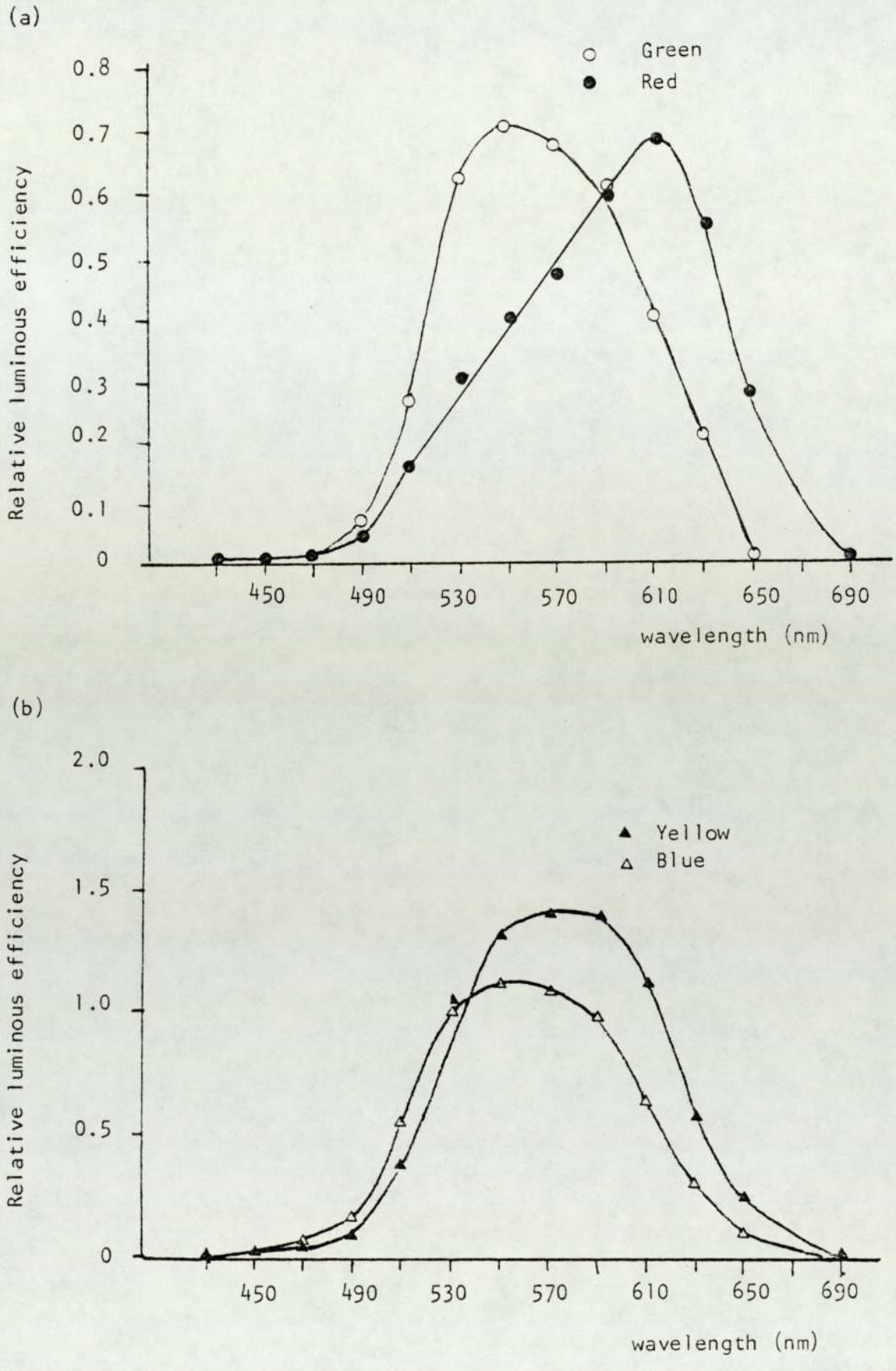


Figure 5

Graph showing the relative luminous efficiency versus wavelength for (a) the red and green squares and (b) the yellow and blue squares

Study on colour defective subjects

Five male colour defective subjects ($\bar{x}$ = 38.8 $\pm$ 12.8yr) with VAs of at least $^{6}/_{6}$ in each eye, were examined on the following tests for colour vision:

1) the Farnsworth Dichotomous Panel D15 test
2) the Farnsworth Munsell 100 Hue test
3) the Ishihara pseudiosochromatic plate test (14th edition)

and 4) the AO-HRR pseudoisochromatic plate test (2nd edition)

Three subjects were classified as being medium deutans, one as being strongly deuteranomalous and the other subject had a generalized colour deficiency around the whole spectrum and not a definite colour defect.

Their total error scores on the FM100 Hue test were 192, 137, 223 and 129 with midpoints of 60, 62, and 56 respectively (the fourth defect was non-specific). The total error score of one subject could not be determined as he could not discern any hue differences between cap no. 10-22 (hues of yellow).

The VERs of these subjects were obtained for pattern reversal and pattern onset-offset stimulation for black/white and coloured stimulation, employing the same stimuli which have been used for the rest of this project. The peak latencies have been analysed by the Fisher-Yates test of significance and the amplitudes by two-way

ANOVA. For the peak latency, the criterion for success is that the latency should be within two standard deviations from the mean. The criterion for failure is that the peak latency lies above two standard deviations of the mean. It is thought that two standard deviations should be used instead of three standard deviations as the proportion of scores falling within the normal distribution is increased by a small percentage, that is, from 97.72% to 99.87% (Miller 1975). By using three standard deviations, the upper limit of normality is substantially increased for the peak latencies, hence excluding possible pathological cases of early onset. The lower limit of normality would also be so low, that it would be hardly likely that the component falling outside this limit would be the one that is being measured, in addition to which, there is no known pathological conditions which gives rise to an early peak latency.

Results

On inspecting Table 40, it can be seen that the peak latencies for pattern reversal red/green 56' and 14' stimulation ($p < 0.024$) are significantly delayed in comparison to those for black/white 56' and 14' and blue/yellow 56' stimulation. The amplitudes of the N2P2 configuration failed to reach significance for any form of pattern reversal stimulation.

The VERs of one of the medium deutans are presented for black/white and red/green 56' and 14' stimulation in Figure 6.

There was one subject who gave responses which are delayed for all forms of pattern onset-offset stimulation with a positive peak

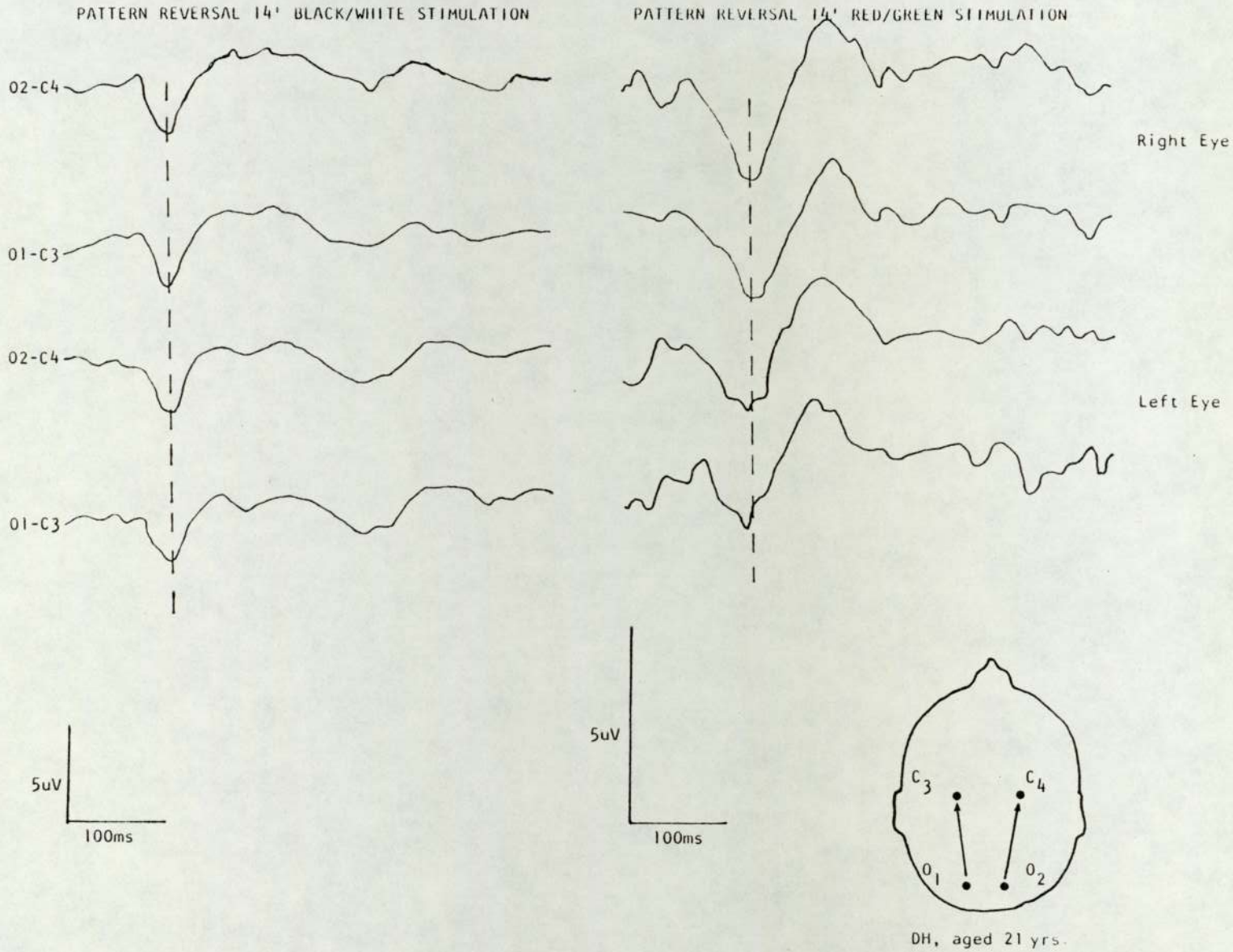


Figure 6 The VERs to pattern reversal 14' black/white and red/green stimulation in a deuteranopic subject whose responses to the latter form of stimulation demonstrated a delay in the latency of the P2 component

Type of Stimulus	Right Eye	Control Subject	Colour Defective	Significance Level	Left Eye	Control Subject	Colour Defective	Significance Level
PR 56' B/W	Normal Abnormal	5 0	5 0	NS	Normal Abnormal	5 0	5 0	NS
PR 14' B/W	Normal Abnormal	5 0	5 0	NS	Normal Abnormal	5 0	5 0	NS
PR 56' R/G	Normal Abnormal	5 0	1 4	$p < 0.024$	Normal Abnormal	5 0	1 4	$p < 0.024$
PR 14' R/G	Normal Abnormal	5 0	1 4	$p < 0.024$	Normal Abnormal	5 0	1 4	$p < 0.024$
PR 56' B/Y	Normal Abnormal	5 0	3 2	NS	Normal Abnormal	5 0	3 2	NS

Key: PR - Pattern Reversal; B/W - black/white; R/G - red/green; B/Y - blue/yellow

Table 40 Showing the number of P2 peak latencies which fall within or beyond normal limits for 5 control subjects and 5 colour defective subjects.

occurring at 190 ms for 56' black/white stimulation and was therefore excluded from the analysis. However, the responses for black/white pattern reversal stimulation were within normal limits.

Since one subject was excluded from the data analysis and another subject who was included in the analysis only had a weak colour deficiency, the results for pattern onset-offset stimulation failed to reach sigificance although it can be seen from Table 41, that 3 of the 4 subjects portrayed delayed responses for red/green stimulation (Figure 7).

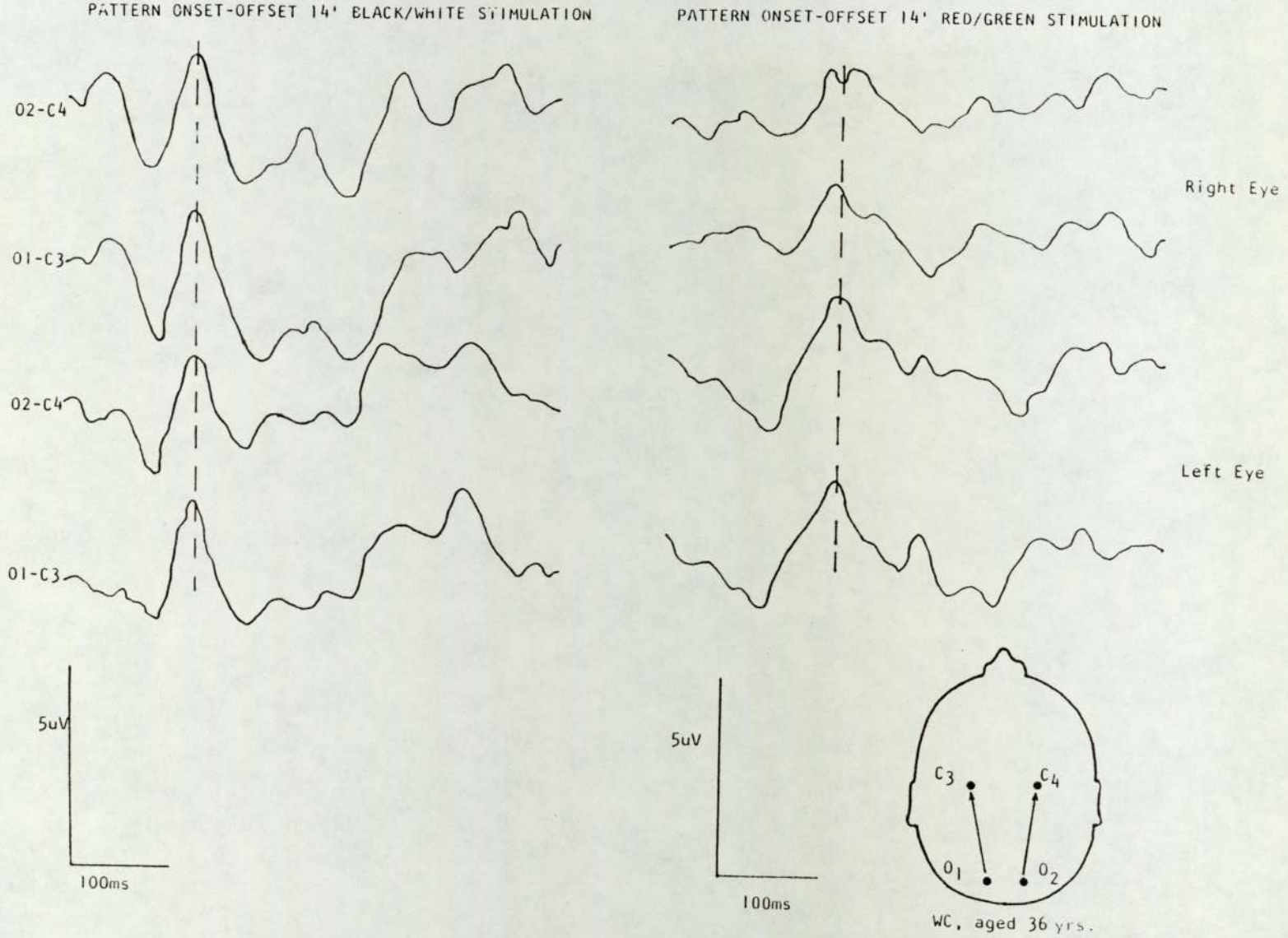


Figure 7 The pattern onset-offset 14' black/white and red/green stimulation of a deuteranopic subject whose responses to the latter form of stimulation demonstrated a delay in latency of the CII component

Type of Stimulus	Right Eye	Control Subject	Colour Defective	Significance Level	Left Eye	Control Subject	Colour Defective	Significance Level
PO/N N56' B/W	Normal	4	4	NS	Normal	4	4	NS
	Abnormal	0	0		Abnormal	0	0	
PO/N N14' B/W	Normal	4	3	NS	Normal	4	3	NS
	Abnormal	0	1		Abnormal	0	1	
PO/N N56' R/G	Normal	4	1	NS	Normal	4	1	NS
	Abnormal	0	3		Abnormal	0	3	
PO/N N14' R/G	Normal	4	1	NS	Normal	4	1	NS
	Abnormal	0	3		Abnormal	0	3	
PO/N N56' B/Y	Normal	4	2	NS	Normal	4	2	NS
	Abnormal	0	2		Abnormal	0	2	

Key: PO/N Pattern Onset/Offset

Table 41 Showing the number of CII peak latencies which fall within or beyond normal limits for 4 control subjects and 4 colour defective subjects.

APPENDIX 10

THE VISUAL EVOKED RESPONSE AND VISUAL PSYCHOPHYSICS DURING ETHAMBUTOL THERAPY

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Since Carr and Henkind (1962) first reported a deterioration in vision in patients being treated with Ethambutol for tuberculosis, many subsequent workers have performed studies to investigate the nature and severity of these visual disturbances (Leibold, 1966; Schmidt, 1966; Roussos and Tsolkas, 1970; Koliopoulos and Palimeris, 1972; Babel et al. 1977; Karmon et al. 1979; Zrenner and Kruger, 1981; Hennekes, 1982). However, to the best knowledge of the authors, no previous workers have observed visually symptomless tuberculotic patients using both electrophysiological and psychophysical tests during the course of treatment on an allegedly safe dose regimen.

The study was designed to examine patients before, during and after treatment with Ethambutol which has been widely-documented as giving rise to visual defects. The triad of drugs which were administered to the patients in this investigation, are Ethambutol, Isoniazid and Rifampicin. The visual disturbances due to Ethambutol and to a lesser extent Isoniazid are said to be dependent on the dose and period of administration (Leibold, 1966; Place et al. 1966; Meyer and Hoigne, 1980) and for these reasons the participating physicians have prescribed the minimum dose of these drugs (15-20 mg/kg Ethambutol; 4-6 mg/kg Isoniazid). In the case of Ethambutol, treatment is usually continued for the shortest possible period (approximately 2 months) as there have been affected cases with even these low dosages (Roussos and Tsolkas, 1970; Friedmann, 1970; Bouzas et al. 1971; Koliopoulos and Palimeris, 1972;

MRC, 1973). The recommended dosage for initial treatment is 15 mg/kg and for retreatment, 25 mg/kg for 60 days followed by 15 mg/kg (Martindale, 1977). For the latter dose regimen, it has been reported that an abrupt loss of vision has occurred within a few months, taking up to 2 years to partially or wholly recover (Bronte-Stewart et al. 1976).

METHOD

Fifteen patients, consisting of ten females and five males with ages ranging between 15-58 years ($\bar{x}$ = 32.3 years) participated in the study. There were two Caucasians, one West Indian and twelve Asians, of which six were non-English speaking.

All patients were investigated on three occasions. The first investigation was performed prior to treatment; the second investigation took place approximately 8 weeks after the commencement of treatment whilst the patients were still receiving all three drugs; the third investigation was carried out approximately 8 weeks after the cessation of Ethambutol treatment but during the continued administration of the other two drugs. The mean dose levels of the drugs were 15.27 $\pm$ 1.87 mg/kg Ethambutol, 5.18 $\pm$ 1.07 mg/kg Isoniazid and 9.21 $\pm$ 1.57 mg/kg Rifampicin.

At each investigation, visual acuities were noted and visual fields and macular thresholds were assessed using the Friedmann Visual Field Analyser, Mark II (the latter two tests were performed on the second and third visits only). Flicker modulation thresholds were determined for 3 separate frequencies, photopic and scotopic electroretinograms (ERG) were recorded.

Visual evoked potentials (VEP) were obtained from electrodes over the right and left visual cortices referred to ipsilateral rolandic sites (O2 - C4; O1 - C3). The signal was recorded on a Mingograf 8-channel EEG machine and the responses were averaged and displayed using a PDP8E computer. The bandpass of the system was 0.5-30Hz. The VEPs were elicited using 6 different stimuli as shown below:-

1 Flash stimulation using a Grass photostimulator at intensity 2 (1363 cd/m^2).

2 Pattern reversal stimulation using a checkerboard with a field size of 25^o, with individual checks subtending 56' for black/white, red/green and blue/yellow colour combinations. In addition to this, checkerboards subtending 3^o with 14' checks were used for black/white and red/green. The coloured checks were matched for equal luminance by heterochromatic flicker photometry whereas the black and white checks had a contrast of 80%.
All stimuli were delivered twice per second in a dimly-lit room (16.5 cd/m^2).

RESULTS

The latency and amplitude of the major positive P2 component were measured and any variation during the three visits analysed using an ANOVA program. All stimuli elicited an increased latency of the P2 (P125 for flash; P100 for pattern reversal) component at the second visit, that is during Ethambutol treatment (Table 1). However, only the flash response ($p < 0.01$) and the pattern reversal response to small check sizes (14') for black/white and red/green ($p < 0.05$) reached significance. All patients showed similar changes in each eye and only

the results for the right eye are shown.

The responses to flash stimulation revealed a marked increase in latency beyond the normal limits for the age in three subjects (Figure 1). In every case, the latency improved on the third visit following cessation of Ethambutol treatment.

The change in latency to the smaller check sizes was less significant than to flash and only two patients showed a marked change although the latencies did not fall outside normal limits (Figure 2). One of the patients demonstrated a marked deterioration in the VEPs with a reduction in amplitude of the N2-P2 configuration and a general change in the morphology of the VEP. In spite of some improvement following cessation of Ethambutol, the VEPs had still not returned to their previous state (Figure 3). This type of change was not seen in any other patient.

With the exception of the flash, there were no consistent changes in amplitude (Table 2). The flash response showed a significant reduction ($p < 0.01$) in the amplitude of the N2-P2 configuration (Figure 1). In view of the changes seen in the VEPs, it is surprising that the parameters of psychophysical testing did not yield any significant differences. Indeed, the only other change observed which was again electrophysiological was the latency of the B wave of the photopic ERG to red stimulation ($p < 0.05$).

DISCUSSION

It is somewhat surprising that the flash responses appeared more sensitive than the pattern reversal response to the subclinical effects

of Ethambutol treatment. However, it has been previously suggested that the flash response is altered in toxic states (Harding et al. 1980) and it has been reported to be just as sensitive as pattern reversal in the detection of neuropathies (Kriss et al. 1982). In addition to this, flash has been found to be a more sensitive indicant of optic atrophy in hereditary conditions (Harding et al. 1979).

The exact mode of action of Ethambutol on the visual system is not known although it has been postulated that the high concentration of zinc found in the optic nerve and retina may be necessary for normal axoplasmic transport and Ethambutol and Isoniazid may make the zinc unavailable by acting as a chelating agent (Edstrom and Matisson 1975; Yolton, 1981). At very high dose levels, demyelinating lesions have been found in the optic chiasma, tract and nerve (Schmidt, 1966).

It should be noted that all latency delays observed during Ethambutol treatment show some improvement following cessation of that drug. The dosage of the drug used was well within the normal therapeutic range and was thought to be below the dosage at which complications normally arise (Meyer and Hoigne, 1980). The patients in this series were treated at a mean dose level of 15.25 mg/kg (SD $\pm$ 1.87 mg/kg). There was no association between the latency of the P2 component and the serum levels.

These electrophysiological findings may provide an explanation for the severity and persistence of the abrupt visual symptoms which have occurred with Ethambutol treatment. If subclinical changes in visual performance are present but are not demonstrable by psychophysical testing then the accumulated deficits eventually become suprathreshold

leading to abrupt and severe symptoms. Such symptoms would then quite logically be relatively intractable and demonstrate slow recovery (Bronte-Stewart et al. 1976).

MEAN LATENCY AND STANDARD DEVIATION OF THE P2 (P100) COMPONENT

(RESULTS ARE SHOWN FOR RIGHT EYE ONLY)

TYPE OF STIMULUS	VISIT 1 (MS)	VISIT 2 (MS)	VISIT 3 (MS)	NO OF SUBJECTS	
Flash	128.80 ± 5.71	135.12 ± 11.85	132.71 ± 8.32	15	P < 0.01
PR 56' B/W	101.55 ± 5.68	103.10 ± 5.53	102.57 ± 4.59	15	NS
PR 14' B/W	103.48 ± 6.34	107.09 ± 8.05	105.73 ± 5.51	14	P < 0.05
PR 56' R/G	108.88 ± 6.34	111.88 ± 7.71	109.77 ± 7.19	15	NS
PR 14' R/G	105.05 ± 7.86	110.29 ± 12.02	108.68 ± 10.53	14	P < 0.05
PR 56' B/Y	106.22 ± 7.02	107.80 ± 7.87	106.82 ± 7.49	15	NS

TABLE 1 B/W - black/white R/G - red/green B/Y - blue/yellow

MEAN AMPLITUDE AND STANDARD DEVIATION OF THE N2 P2 CONFIGURATION

TYPE OF STIMULATION		VISIT 1 (uV)	VISIT 2 (uV)	VISIT 3 (uV)	
FLASH		7.24 ± 3.52	5.39 ± 2.15	5.69 ± 2.24	P<0.01
PR 56'	B/W	5.90 ± 3.12	5.77 ± 2.40	4.64 ± 2.27	NS
PR 14'	B/W	2.97 ± 0.86	3.42 ± 1.60	3.07 ± 0.72	NS
PR 56'	R/G	4.24 ± 2.49	3.56 ± 1.27	3.49 ± 1.16	NS
PR 14'	R/G	3.03 ± 1.08	3.03 ± 1.07	2.95 ± 0.73	NS
PR 56'	B/Y	3.51 ± 1.93	3.51 ± 1.69	3.24 ± 1.20	NS

TABLE 2

POSITIVITY IS DENOTED BY DOWNWARD DEFLECTION

LEGENDS FOR FIGURES

FIGURE 1

The responses to flash stimulation for each visit, showing an increase in latency of the P2 (P129) component and a reduction in amplitude of the N2-P2 configuration whilst on therapy. On the third visit after cessation of Ethambutol, there is some improvement although the VEP has not returned to its original state. Patient and treatment details as shown.

FIGURE 2

Responses to pattern reversal stimulation using a small check size, demonstrating an increase in latency of the P100 component on the second (during treatment) and third (post Ethambutol) visits. Although the P100 component was delayed, it never exceeded normal limits for the age.

FIGURE 3

Pattern reversal responses of a patient who demonstrated a marked deterioration in the VEPs with a reduction in amplitude of the N2-P2 configuration and a general change in the morphology during treatment. Similar changes were seen in all responses to a variety of pattern reversal checkerboards and also to flash. Following Ethambutol withdrawal there is some improvement in the P100 component.

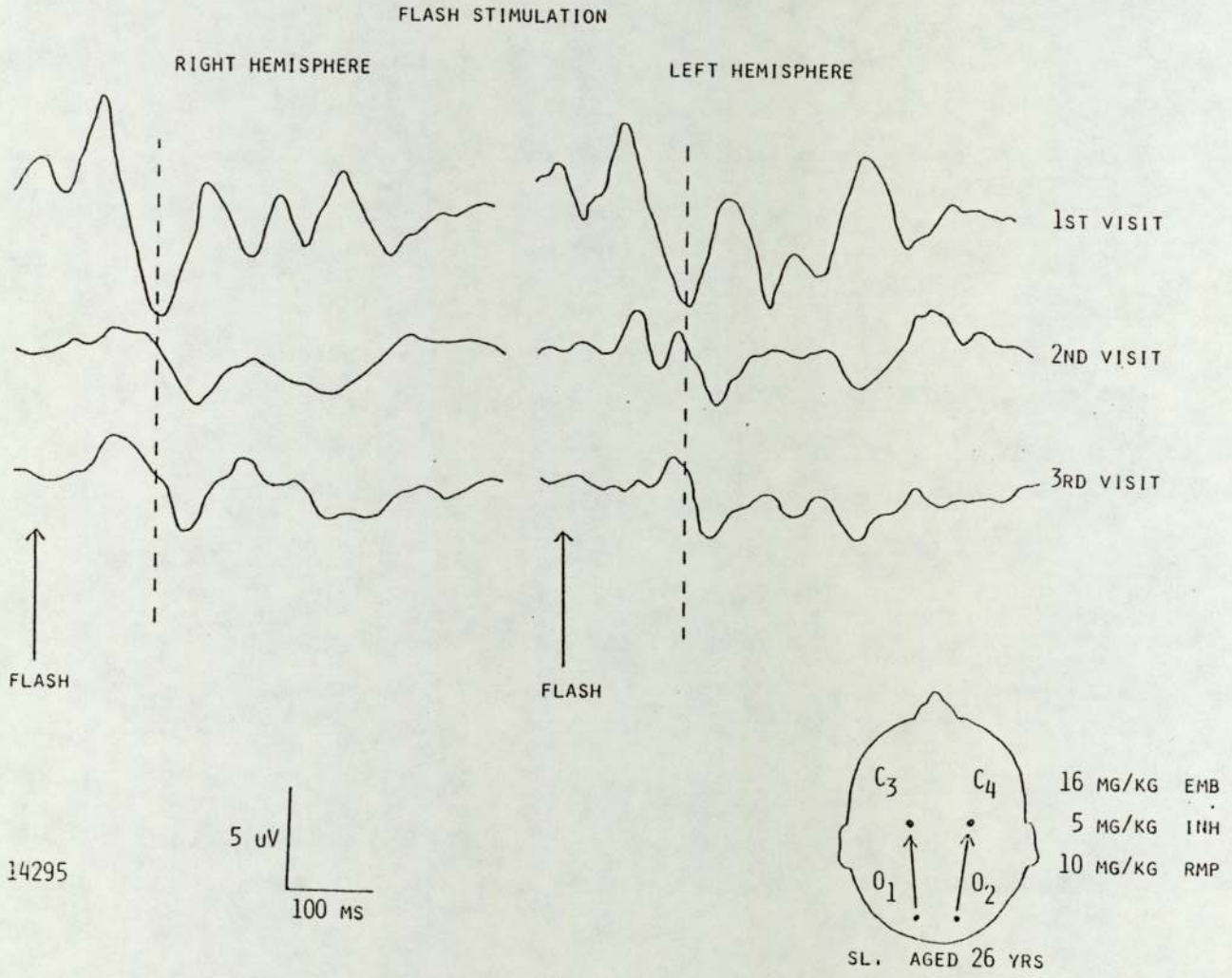
FLASH STIMULATION
RIGHT HEMISPHERE
LEFT HEMISPHERE
1ST VISIT
2ND VISIT
3RD VISIT
FLASH
FLASH
5 uV
100 MS
14295
C3
C4
O1
O2
16 MG/KG EMB
5 MG/KG INH
10 MG/KG RMP
SL. AGED 26 YRS

Figure 1

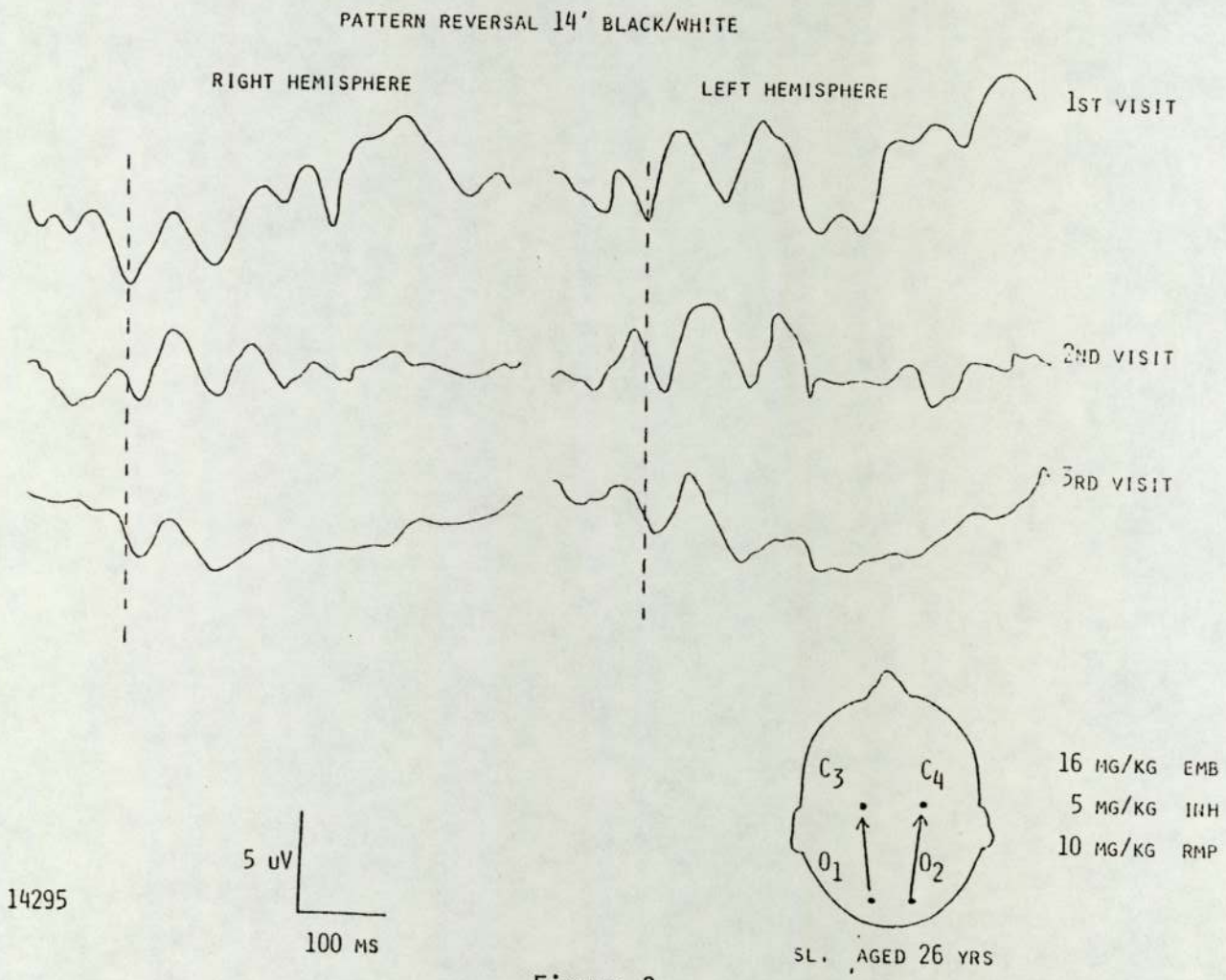
PATTERN REVERSAL 14' BLACK/WHITE
RIGHT HEMISPHERE
LEFT HEMISPHERE
1ST VISIT
2ND VISIT
3RD VISIT
5 uV
100 MS
14295
C3
C4
O1
O2
16 MG/KG EMB
5 MG/KG INH
10 MG/KG RMP
SL. AGED 26 YRS

Figure 2

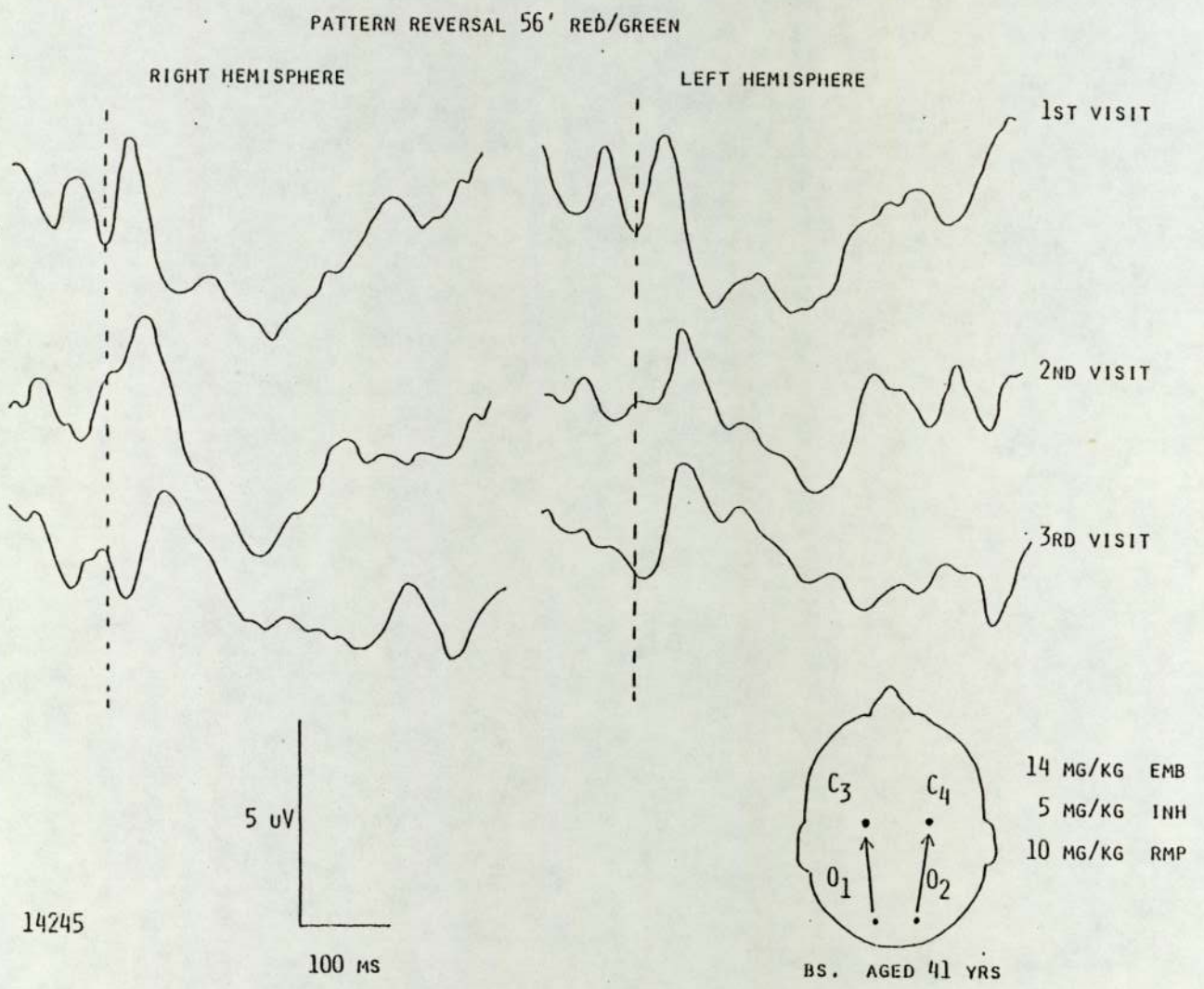
PATTERN REVERSAL 56' RED/GREEN
RIGHT HEMISPHERE
LEFT HEMISPHERE
1ST VISIT
2ND VISIT
3RD VISIT
5 uV
100 MS
14245
C3
C4
O1
O2
14 MG/KG EMB
5 MG/KG INH
10 MG/KG RMP
BS. AGED 41 YRS

Figure 3

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