AN INVESTIGATION INTO THE STIMULUS CHARACTERISTICS IN PHOTOSENSITIVE EPILEPSY WITH A REGARD TO THERAPEUTIC PROCEDURE

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

BY

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SUMMARY

The objectives of this investigation were to determine the effects of stimulus parameters on photosensitivity and that of therapeutic measures using sodium valproate (Epilim (R)), thereby obtaining further insight into the characteristics and operation of photosensitive epilepsy.

The most provocative stimulus in eliciting the photoconvulsive response (PCR) was found to be a fine flashed-on grid pattern. The photosensitive visual evoked potential (VEP) was enhanced by optimal stimulation of the macular.

Standard antiepileptic drugs had no beneficial effects on photosensitivity and, before sodium valproate treatment, some patients still exhibited photosensitivity even after 12 years from onset.

Fifty photoconvulsive patients, ranging in age from 6 - 25 years, were referred for investigation from hospitals in the Birmingham area. Recording was made of the basic and photically activated EEG and the VEP before and during sodium valproate treatment. Sixteen patients were similarly investigated after drug withdrawal.

Sodium Valproate was found to be particularly effective in the treatment of spontaneous and photically evoked generalised spike and wave abnormalities. Optimum dosage levels were found for each patient, which ranged from 600-1600 mgm. daily with a modal dosage of 1000 mg/day. The majority of patients (78%) showed a significant improvement in photosensitivity after a variable treatment period from 1 month to 2 years 9 months (mean 9 months). The basic EEG showed marked benefit, on average 4.5 months previous to the effect on photosensitivity. Sodium valproate reduced VEP amplitude to some extent but no effect occurred on occipital spikes. The general effect of sodium valproate withdrawal was either a reappearance or increase in spontaneous and photically evoked abnormalities. Clinical findings during treatment were favourable. Overall only 16% of patients showed definite side-effects as a result of sodium valproate therapy.

The results are discussed in relation to the possible pathophysiological mechanisms of photosensitive epilepsy.

Key Words: Photosensitive Epilepsy, Sodium Valproate, Electroencephalogram, Prognosis, Intermittent Photic Stimulation.

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C O N T E N T S

L I S T O F T A B L E S

L I S T O F F I G U R E S

SECTION 1:

LITERATURE REVIEW.

1. INTRODUCTION TO PHOTOSENSITIVITY

1.1. Definition and Incidence in the Population.

Epilepsy is defined as the tendency to have recurrent fits. An attack is caused by a sudden abnormal discharge in the brain cells. This electrical storm may occur in any region of the brain as a result of hyper-excitability in the various sensory or motor modalities. It would therefore be more correct to talk about 'the epilepsies' (Jeavons 1972a). Epileptic attacks may be symptomatic, through structural damage to the brain, or idiopathic, where the cause of epilepsy is uncertain.

The incidence of epilepsy in the general population has been quoted as 0.5% (Lennox 1947; Jeavons 1972a) with a slightly higher frequency in children of 0.7 - 0.8% (Cooper 1965; Jeavons 1972a). However, epilepsy is often misdiagnosed and these figures may be unduly high. In one report, 20% of patients referred to an epilepsy clinic were not considered as suffering with epilepsy. (Jeavons and Harding 1975).

Many seizures may be regarded as 'reflexive' in nature, i.e. in response to a clearly defined, often stereotyped stimulus (Wadlington and Riley 1965). It is, however, often difficult to specify a single stimulus due to the complexity of the sensory input. Of the total epileptic population, up to 1% are reported as having seizures related to various sensory stimulation (Schmidt and Wilder 1968). Auditory stimulation is most effective in animal species other than man (Watson and Marcus 1962), and generally there is no evidence of structural change in the nervous system. Sight plays a predominant part in the human perceptual world and, as

about 90% of man's sensory input travels along the optic nerves (Smith 1970), it is evidential that the most common form of 'reflex epilepsy' in man is photosensitive epilepsy.

Photosensitive epilepsy has been defined as a pathologic entity characterised by sudden recurring seizures precipitated by intermittent visual stimuli (Hess, Harding and Drasdo 1974). The incidence of photosensitivity in the general population is difficult to estimate as percentages in the literature tend to be based on selective studies. Also, many authors do not describe the types of responses which they classify as abnormal and a wide variety of photic stimulation methods are employed (Jeavons 1969). An added problem is the failure to differentiate between photosensitivity and photosensitive epilepsy.

Several authors have published figures for the incidence of photosensitivty in normal subjects which range from 1.33% to 4.4% (Mundy-Castle 1953; Herrlin 1954; Gastaut, Trevisan and Naquet 1958; Ulett and Johnson 1958). A very high incidence (25.5%) of photically evoked EEG abnormality was reported by Brandt, Brandt and Vollmond (1961) from a sample of 150 non-epileptic children. Of these, 14.2% showed generalised spike and wave discharge. It is noticeable that these authors presented an unusually prolonged, intermittent photic stimulation (IPS) lasting 6 minutes.

Other studies quote the incidence of photosensitivity either from routine consecutive EEGs or for selected epileptic samples. Lloyd-Smith and Henderson (1951) found that 21.6% of epileptic patients showed photically induced EEG paroxysms which at times were associated with myoclonic jerks or generalised seizures. However, IPS was not standardised and lasted up to 3 minutes. Using a photic stimulation period of up to 20 minutes, Herrlin (1954) observed

'pathological cerebral activity' in 18.8% of suspected epileptic children up to 15 years of age with accompanying clinical seizures in 3%. Generalised spike and wave was evoked in 15% of a large epileptic population (Gastaut et al. 1958). However, when primary generalised epileptics were considered alone, this incidence increased to 25%. Similarly, Melsen (1959) found photically evoked abnormalities in 24.7% of patients with idiopathic epilepsy and in 6.7% with symptomatic epilepsy. Examination of consecutive routine EEGs by several authors revealed an occurrence of epileptiform responses during IPS in 3% of patients (Hughes 1960); 6.8% of patients without seizures and in 11.6% of epileptics (Watson and Marcus 1962); 250 out of 20,000 EEGs of which 25 showed clinical accompaniment (Wadlington and Riley 1965); 11% of 6403 routine cases (Capron 1966). Jeavons (1966) observed spike and wave abnormality in 2.8% of 14,141 routine patients of which only 0.12% had photosensitive epilepsy, i.e. 17% of the photosensitive cases.

Photosensitive epilepsy was found to occur in 2-4% of all patients attending an epilepsy clinic (Bickford and Klass 1969) although it is believed to be more common than pure petit mal epilepsy (Jeavons 1972a). In a catchment area of 5 million people Jeavons and Harding (1975) reported a 0.01% incidence of photosensitive epilepsy in the overall population, which increased to 8% in an epileptic population investigated over 12 years.

The incidence of epilepsy is slightly higher in children than adults and so it follows that the incidence of photosensitive epilepsy may also be greater. The onset of this condition was found in 66% of patients between the ages of 5 to 14 years (Jeavons and Harding 1975). In 1968 the

U.K. population figures showed that this age group constituted about 15% of the general population. Recalculation of these authors' figures produces an incidence of photosensitive epilepsy onset in the order of 0.04% for 5 to 14 year olds and 0.004% after 15 years of age. Therefore, photosensitive epilepsy is about ten times more likely to originate during childhood than adulthood.

1.2. Early History.

Epilepsy was supposedly first described by Hippocrates (400 B.C.) as being seated in the brain and consisting of 'an overflow or superfluity of phlegm' which induced an attack when rushing into the bloodstream (Lennox 1947; Hess et al. 1974). Early beliefs that light was a precipitator of epilepsy was due to the apparent implication of the sun in changing the consistency of the brain, thus leading to an attack (Panayiotopuolos 1972). The most frequently quoted early reference is that made by Apuleius in his book 'Apologia' (circa 125 A.D.) and this has led to some controversy due to certain authors embellishing on the original account (Mawdsley 1961; Harley, Baird and Freeman 1967; Brausch and Ferguson 1965; Troupin 1966). In fact, Apuleius makes no reference flickering light .....'the spinning of a potter's wheel which would easily infect a man suffering from this disease (i.e. epilepsy) with its own giddiness' (Butler's translation 1909). Potters' wheels at that time were not spoked and a more likely explanation of the effects induced by gazing at a potter's wheel was suggested to be vertigo and sickness (Panayiotopoulos 1972). An even earlier reference (circa 2 A.D.) by Soranus of Ephesus was cited by Schwartz (1962) ....'when a case of epilepsy is in its quiescent stage, the untimely use of light may cause the recurrence of an attack'. However, the first scientific evidence of photosensitive epilepsy is from Gowers (1885). He described the case of a girl with attacks in bright sunlight and that of a man who had an aura of blue lights followed by a convulsion when he viewed bright lights.

The advent of electroencephalography in the 1930's introduced early techniques of photic activation. Adrian and

Matthews (1934) were able to evoke photic following of occipital brain rhythms at flicker rates up to 25 f.p.s. using an illuminated glass bowl and a disc with cut out sectors. Walter, Dovey and Shipton (1946) developed an electronic stroboscope for clinical use. They showed that specific EEG patterns were affected by objective and subjective alterations during photic stimulation. It was also capable of evoking'brief larval seizure discharges' in a drug controlled patient. Refinements of automatic analysis and averaging techniques after the 1950's, together with the widespread use of IPS as an activating technique, enabled investigations into the causes, characteristics and possible remedies of photosensitivity.

1.3. Precipitating Factors.

Photosensitive epileptics are vulnerable to bright and flickering light within the everyday environment. This also includes various artificial light sources. Bright continuous sunlight by itself or reflected on windows or glass has been reported as a precipitant of fits (Goodkind 1936; Forster and Campos 1964; Jeavons and Harding 1975). These attacks usually take the form of myoclonic jerking, disturbances in consciousness or even generalised seizures. Even when fits do not occur, many photosensitives may experience nausea, giddiness or headaches. Bickford and Kłass (1969) suggested that attacks in continuous light were in fact due to the light becoming flicker through rapid blinking. However, flickering light can also be caused by reflections off the sea, wet streets, swimming baths, snow and car windscreen (although the latter two are probably more likely to produce glare). All these conditions have been cited in relation to fits (Daly and Bickford 1951; Courjon 1955; Harding, Drasdo, Kabrisky and Jeavons 1969; Jeavons and Harding 1975).

Flickering sunlight may also act as a precipitant when patients are travelling through an avenue of trees and past railings or houses with the sun shining behind them (Cobb 1947; Daly and Bickford 1951; Courjon 1955; Pantelakis, Bower and Jones 1962). Sunlit reflections off uneven surfaces, viz. rippling water or through decorative glass introduces an added factor of pattern. Goodkind (1936) noticed that sunlight through a window covered with wire mesh caused severe myoclonic jerking in his patient. Bickford, Daly and Keith (1953) observed 'staring spells' in a 6 year old boy when he gazed at patterned cloth or screens. Striped

cloth, floor grills, fences and riding escalators were effective triggers in eight patients (Jones, Andermann and Wilkins 1976). Jeavons and Harding (1975) report the case of one patient sensitive to moving escalators and windscreen wipers. Another patient suffered with myoclonic jerks when gazing at the garage doors at home, painted in black and white alternate stripes. These attacks also occurred when he looked up through leaves on trees, again on bright days, and also when his bedroom light was switched on in the morning. Such a sudden change from dark to light is provocative in some patients (Bower 1963).

Flickering light arising from anti-collision beacons reflecting intermittently, particularly at night, can be annoying to pilots (Johnson 1963). Also sunlight reflected off rotor blades and propellors of aircraft have caused symptoms of discomfort, blurred vision, nausea and dizziness (Johnson 1963; Chorley 1972). This was termed 'flicker vertigo'. However, in some cases severe panic and even unconsciousness have occurred. Testing pilots with IPS revealed an effective range between 8 - 24 f.p.s. which falls within the f.p.s. rate of a propellor at idling speeds (Chorley 1972). This author proposed that a three-bladed helicopter propellor rotating at 300 r.p.m. would produce a flicker rate of 15 f.p.s. Painting the blades black to reduce the sun's reflections proved ineffective, showing that the crucial factor was the intermittency of the light source.

Artificial light sources, e.g. arc lights (Cobb 1947) fluorescent lighting (Bower 1963; Brausch and Ferguson 1965; Jeavons 1972b) and stroboscopic light such as in discotheques and shops (Cobb 1947; Jeavons 1972b; Jeavons and Harding 1975) are potentially hazardous to the photosensitive patient.

Richter (1960) reported the rarity of epileptic fits at the cinema in comparison to television viewing. He attributed this to the flicker frequencies of 48 - 72 c.p.s. of the cinema screen being too high to evoke paroxysms and the intensity of the screen being lower than that of television. However, home made ciné films are often shown at a rate which will provoke seizures, usually between 16 - 24 c.p.s. (Bower 1963; Troupin 1966). Although photosensitive patients are at risk, therefore, when watching home movies, fits under these circumstances are rare because home ciné equipment is uncommon.

1.3.1. Television epilepsy.

Television is the most frequently reported artificial light precipitator of photosensitive seizures. The earliest account in the literature appears to be by Ismay (1958) who described the case of an electrician having tonic-clonic fits when rectifying faulty television sets. Klapetek (1959) later described similar incidents in a 12 year old boy and warned of the possible 'photogenic provocation' of epileptic seizures in children with the spread of television over the world. It was estimated that 90% of children between 5 and 15 years of age live in households with television sets and spend on average 2.75 hours in daily viewing (Bower 1963). Nowadays programmes are screened for about 90 hours per week (Binnie, Darby and Hindley 1973). It is therefore possible that an attack in front of the television is unrelated to it and occurs by chance. Gastaut, Regis, Bostem and Beaussart (1961) estimated that only 25% of supposed television-induced seizures were definitely due to television acting as a photic stimulus. Attacks generally occurred during the evening when the patient tended to be drowsy, and after 2-3 hours of viewing time. The authors believed illness, excitement, alcohol,

fatigue and premenstruation could be involved. Hypoglycaemia was also noted to be an implicating factor (Charlton and Hoefer 1964). The incidence of television-induced epilepsy was found to be 5.7% of 4-15 year old epileptic children, although some also had spontaneous fits (Pantelakis et al. 1962). A detailed study by Jeavons and Harding (1975) showed that just over half of their photosensitive patients only had fits while watching television, the remainder having seizures of a different nature.

Many authors cite defective television sets as the prime cause of 'television epilepsy'. Either the screen flickered or the vertical hold was faulty, making the picture roll (Mawdsley 1961; Pallis and Louis 1961; Troupin 1966; Ames and Pietersen 1972; Binnie et al. 1973). Pantelakis et al. (1972) distinguished between two groups of patients; a very sensitive group to IPS had convulsions while viewing the television at a reasonable distance, and a less sensitive group had seizures when either the picture was faulty or when they sat too close to the screen. Prolonged and mainly close viewing in a dimly lit room, adjusting the controls or switching channels particularly in front of a brightly illuminated screen appear to be potent factors in provoking seizures (Mawdsley 1961; Pallis and Louis 1961; Troupin 1966; Jeavons and Harding 1970; Hess et al. 1974).

Close viewing was the prime cause of fits in 60% of patients with purely television-induced seizures and in 34% of patients who also had spontaneous attacks (Jeavons and Harding 1975). It was suggested that sensitivity to flickering light from the screen increased directly with the increasing area of peripheral retina stimulation, which would obviously depend on

proximity to the television (Pantelakis et al. 1962; Charlton and Hoefer 1964). The peripheral retina was also considered to be more flicker sensitive than the macula and so the patient would be at risk when viewing at an angle. However, only 5 out of 299 television epileptics were found to have had a fit when viewing from an angle and probably when too near the set (Jeavons and Harding 1975). Even though flicker may not be perceived by direct viewing of the television screen, the sensitive retinal areas are still being stimulated. Proximity to the television allows the eye to resolve the line details more easily. In Europe the television screen flickers at the mains frequency of 50 c.p.s. and, although Gastaut et al. (1961) did not find convulsive responses in the EEG at frequencies above 40 f.p.s., others have found flash rates up to 50 f.p.s. and over capable of inducing spike and wave discharges (Pantelakis et al. 1962; Jeavons and Harding 1975). Close viewing and interference shows up the television scanning lines as two stimuli, each at 25 c.p.s., which are out of phase (Moiré patterns). A loss in vertical hold will also produce a 'flicker effect' at 10-25 c.p.s. (Troupin 1966) and it is generally accepted that 10-25 f.p.s. IPS is particularly effective for EEG activation (Bower, 1963; Troupin 1966; Jeavons and Harding 1970). Most of the literature quotes a lower incidence of 'television epilepsy' in the U.S.A. There the mains frequency is 60 c.p.s. which produces half-scans of 30 c.p.s. believed to be less epileptogenic. However, Jeavons and Harding (1975) found that 72% of photosensitives responded to 30 f.p.s.

Most authors confirm a diagnosis of 'television epilepsy' from the appearance of spike and wave discharges during laboratory IPS. A high correlation was found

between EEG findings during IPS and clinical seizures with television (Pantelakis et al. 1962). A few authors have actually investigated the EEG responses when their patients watched television. Gastaut, Regis, Bostem and Beaussart (1960) could not evoke EEG abnormalities in any patient under normal or maladjusted viewing conditions. This may have been due to the use of high quality equipment supplied by Radio Télévision Francaise (Binnie et al. 1973). Spike and wave paroxysms were only found in 1 out of 12 patients as a result of changing channels (Dumermuth 1961). However, using domestic black and white sets, Binnie et al. (1973) induced spike and wave in 9 out of 10 patients under normal viewing conditions and in 5 patients when seated at a distance from the television. A similar finding was reported by Darby and Hindley (1974). They also found that increasing the contrast and brightness level had little influence, but an unstable vertical or horizontal hold increased the probability of spike and wave in patients viewing at distances which, under normal conditions, had no effect. A well adjusted set was capable of evoking spike and wave in a patient seated 0.5 to 4 metres away from the screen. They postulated that the main cause of television induced seizures was not moving screen images, nor line and frame frequencies, nor gross malfunction of the set, but minor instabilities in the system producing low frequency flicker spontaneously or from faults in line synchronisation in areas of poor reception. Connell, Jolley, Lockwood and Mercer (1975) reported that a settled colour picture was less activating than a black and white, but that a distorted colour picture was equally as effective. They found spike and wave discharge through move-

ments occurring in a controlled picture of a black and white set and therefore suggested that the contrast of moving patterns was implicated in the activating effect of television.

Several authors have shown that black and white geometric patterns enhance or evoke spike and wave activity in the EEG (Bickford and Klass 1969; Chatrian, Lettich, Miller and Green, 1970a; Jeavons, Harding, Panayiotopoulos and Drasdo 1972b). Although Gastaut et al.(1961) found cartoons to be effective in triggering attacks in three patients and similarly, quickly changing advertisements in one patient, others found no direct relationship between the recurrence of fits and particular types of programme (Bower 1963; Jeavons and Harding 1975). However, the latter authors noticed that in three patients fits had occurred when watching 'Top of the Pops' on black and white screens that would highlight the 'Op-Art' patterns commonly seen in that programme. Darby, Binnie, Harding, Jeavons, Stefannson and Wilkins (1977) found that 70% of photosensitive patients showed EEG paroxysms when viewing a normally functioning television but in an area of poor reception. 'Line-jitter' which is readily seen on old black and white screens, particularly under conditions of low signal strengths, was replicated using oscillating gratings and checkerboard patterns. Sensitivity to this pattern movement was observed in 61% of the patients. It was suggested that the vibratory patterns not only simulated 'line jitter' but were also similar to the process of interlacing, which produces the picture.

'Television epilepsy' mainly occurs in children, although not exclusively (Charlton and Hoefer 1964; Troupin 1966). Gastaut et al.(1961) reported that of 35 affected

patients 53% were aged up to 10 years, 18% were between 11-20 years and 29% between 21 - 40 years. The onset of television induced seizures tends to occur earlier than fits in other photosensitive groups (Jeavons and Harding 1975). It is generally agreed that the most common form of television seizure is a tonic-clonic fit. Other forms may occur, however, e.g. confusional episodes, myoclonic jerking, loss of consciousness, subjective auras, and rarely, typical absences (Bower 1963; Jeavons 1972b; Hess et al. 1974). However, it is possible that in the home absences could go undetected while the child watches television (Charlton and Hoefer 1964).

Gastaut et al. (1961) observed that of 35 patients sensitive to television, 11 had normal EEGs, 3 focal abnormalities, and 21 patients showed generalised spike and wave. A high incidence of abnormal resting records was found by Charlton and Hoefer (1964) but Jeavons and Harding (1970) reported that at least half of their patients with only fits to television had normal EEGs except when exposed to IPS. Spontaneous 3 c.p.s. spike and wave activity had previously been reported as being less common in this type of patient than those also suffering from other forms of seizure (Jeavons 1966).

Although Charlton and Hoefer (1964) found no undue sex predominance in their series, Jeavons and Harding (1975) found a direct relationship in 6 female patients, between television induced seizures, EEG abnormality during IPS, and the menstrual cycle. 'Television epilepsy' was often found to begin around puberty (Jeavons 1972b) but the original cause of these seizures is speculative. Charlton and Hoefer (1964) found that in 9 patients with 'television epilepsy', 4 had a family history of epilepsy and, in 3 cases, infantile epilepsies had

been prevalent. Bower (1963) suggested that a family history of epilepsy was not common in television-sensitive patients, but a family history of migraine or discomfort from flickering lights was more usual.

Some patients report feelings of being 'drawn to the television set like a magnet'. This is described as 'impulsive attraction' (Jeavons and Harding 1970) and such patients tend to start jerking or have an absence seizure as they get close to the screen. All these patients have wide sensitivity ranges to IPS and compared to other television sensitive groups, have significantly more spontaneous spike and wave in their EEGs. More males than females are generally affected with this attraction, unlike the overall ratio in photosensitive epilepsy which is predominated by females. Although all patients in this group are inexplicably drawn towards the television screen, they differ in their subjective sensations. Some enjoy the experience; others want to avoid the set but cannot stop themselves (Jeavons and Harding 1975). In 30 patients with 'impulsive attraction' investigated by these authors, it was evident that 2 patients were purposely using the television screen as a flickering light source, e.g. changing channels in the middle of a programme for no apparent reason. Similar incidents were suspected in 3 other children. Although Bower (1963) found no reports of patients who self-induced attacks, e.g. waving fingers across sunlight, and also had attacks while viewing television, Harley et al. (1967) reported the case of a boy impulsively attracted to the television who self-induced attacks by head nodding and blinking in front of the screen. Rail (1973) discovered another similar case and Jeavons and Harding (1975) described

two self-inducing patients also clinically sensitive to television.

Limiting the amount of viewing or forbidding television is an impractical form of treatment, as patients have been known to conceal details of their seizures if they suspect future restrictions (Pantelakis et al. 1962; Charlton and Hoefer 1964; Ames and Pietersen 1972). Most authors recommend, therefore, that the patient looks away when the set becomes faulty, avoids changing channels, and sits well away from the screen. However, the treatment of this type of epilepsy should depend on whether the patient has fits at other times and whether the basic EEG is normal (Jeavons 1972b). Patients who are clearly photosensitive and in whom fits have occurred with flickering light in the every-day environment are instructed to adopt the following precautions (Jeavons and Harding 1970; 1975) :-

(i) To view the television in a well-lit room, at least 8 feet away, and never to approach, adjust the set or change channels. A small lamp on top of the television helps the relative screen contrast;

(ii) To cover one eye firmly with the palm of one hand, if it is really necessary to approach the set;

(iii) The patient should ideally never attend discotheques and other places where flashing lights are used but, if flashing lights suddenly occur, to cover one eye as in (ii);

(iv) To wear polarised sunglasses out of doors on sunny days to remove flickering reflections. Tinted lenses are insufficient.

1.3.2. Self-induced epilepsy.

Self-induced epilepsy appears to be rarer than classical photosensitive epilepsy (Andermann, Oaks, Berman, Cooke, Dickson, Gastaut, Kennedy, Margerison, Pond, Tizard and Walsh, 1962; Harley et al. 1967). Jeavons and Harding (1975) report that only about 100 cases are cited in the literature.

This form of epilepsy is characterised by the patient precipitating attacks by staring at bright light, notably the sun, and either blinking rapidly, nodding the head rhythmically, hopping up and down,or rapidly waving the out-spread fingers of one hand across the eyes (Bickford et al. 1953; Hutchinson, Stone and Davidson 1958; Andermann et al. 1962; Hutt, Lee and Ounsted 1963; Livingston 1964; Troupin 1966; Ames 1974). Medical referral usually occurs between the ages of 8-12 years (Andermann et al. 1962) although cases of younger and older children have been reported from 2 - 16 years (Hutt et al. 1963; Livingston 1964; Harley et al. 1967; Ames 1974). Self-inducers are predominantly female with a ratio of about 2:1 (Andermann et al. 1962). These authors wondered whether this was an hormonal effect or whether the longer hair of females when flicked out of vision would create photic effects and learned development of further self-induction.

The patient's family history is usually positive for fits, faints, neurological or behavioural troubles (Andermann et al. 1962) and often the child has a difficult home life through neglective or over-protective parents (Hutchinson et al. 1958; Harley et al. 1967). Occasionally the patient may have suffered infantile convulsions or early childhood epilepsy (Andermann et al 1962; Livingston 1964).

The most common form of self-induced seizure is brief but repeated absences; minor or gross myoclonic phenomena may occur and, rarely, major tonic-clonic convulsions (Andermann et al. 1962; Hutchinson et al. 1958; Hutt et al. 1963; Livingston 1964; Forster, Ptacek and Peterson 1965; Troupin 1966; Rail 1973). Varying degrees of consciousness occur within the self-induced attack (Harley et al. 1967). Some authors believe that the eyelid myoclonia and hand-waving action are integral parts of the seizure and not precipitants (Livingston 1964; Ames 1974). Jeavons and Harding (1975) found clear evidence of integrated hand movement in only 1 out of 5 self-inducing patients.

Reports vary as to the intelligence of this type of patient. Half of the published cases are mentally retarded and show slow mental development, (Andermann et al. 1962). The degree of retardation appears to be related to the frequency of seizures rather than the severity, which creates problems in school performance. Most patients also have personality problems which may be linked with the onset of the epileptic condition or arise as a result of punishment or parental restriction because of the attacks (Hutchinson et al.1958). Emotional instability and temper tantrums may be related to mental handicap in some patients (Andermann et al. 1962). The children may be aggressive, hyperkinetic, or spoiled (Hutchinson et al 1958; Harley et al. 1967; Ames 1974) and the attacks may be surrounded by feelings of guilt creating behaviour problems.

Although patients are evasive in their reasons for self-inducing seizures, there is evidence that the action is pleasurable (Andermann et al. 1962). Reward may be in their escape from undesirable situations, attracting attention, punishing those around them or simply inducing a pleasant

sensation (Forster et al. 1965; Troupin 1966; Harley et al. 1967). Pleasurable sensation may result through laboratory IPS (Hutt et al. 1963) and may accompany evoked EEG paroxysms in intelligent and sub-normal non-epileptic children. (Van Steenbrugghe and Lairy 1965).

The EEG of the typical self-inducer has been described as 'dysrhythmic and immature' (Andermann et al. 1962). There is, however, no characteristic feature in the basic EEG although patients vary slightly in their response to IPS. Onset of a seizure is usually indicated by low voltage localised or generalised spikes, leading to bilateral generalised polyspikes and slow waves with gradual development of the slow components (Andermann et al. 1962; Hutt et al. 1963; Ames 1974). Self-induced epileptics have a wide sensitivity range to IPS, the most effective frequencies being 10 - 20 f.p.s. (Andermann et al. 1962). The provocative frequency of 15 f.p.s. is easily achieved by waving the outstretched fingers (Hutchinson et al. 1958).

Testing the short-term memory recall of a few patients, Hutt et al. (1963) found impairment during IPS frequencies which consistently evoked spike and wave complexes. This 'retrograde amnesia' could occur when the paroxysm was unaccompanied by a clinical seizure. It has been proposed that self-induction requires not only hypersensitivity to light but also supersensitivity of parts of the nervous system not involved in visual perception (Andermann et al. 1962). The clouded awareness, compulsion, and pleasurable sensations may involve reward systems in which certain hypothalamic nuclei and parts of the reticular system are involved,

creating a need for repetition of the stimulating action (Hutt et al. 1963; Harley et al. 1967). Stimulation of the reward system may also interfere with the learning process as seen in animal studies (Smith 1970). A conditioned response is usually highly stereotyped in animals and it has been noted that during self-induction hand-waving invariably occurs with the same hand (Hutchinson et al. 1958), but controversy exists as to whether a conditioning effect is incorporated in self-induced epilepsy (Andermann et al. 1962).

Treatment is difficult, as often the patient is reluctant to stop the attacks. Psychotherapy has proved unsuccessful (Hutchinson et al. 1958) and similarly coloured spectacles (Harley et al. 1967). Administration of the oxazolidine-dione group of drugs was recommended which, when combined with the wearing of dark glasses, was supposedly effective in reducing the sensitivity range in some cases (Andermann et al. 1962). Rail (1973) reports complete control of self-induced seizures with clonazepam. As yet, no cases have appeared in the literature of sodium valproate therapy for self-induced epilepsy.

1.4. Group Classification.

Photosensitive patients vary in their clinical and EEG responses to everyday and laboratory photic stimulation. The circumstances under which these responses occur have given rise to several patient classifications. Bickford et al. (1953) distinguished between 3 types of patient :-

(i) A clinically sensitive group where seizures were induced through light of an everyday intensity,

(ii) A less sensitive group in which seizures could only be induced under conditions of high intensity illumination and rapid flicker as produced in the laboratory;

(iii) A group in which no clinical seizures existed in relation to light, the only evidence of photosensitivty being the occurrence of seizure discharge during IPS.

The authors proposed that this classification indicated more than a progressive lowering of the convulsive threshold, as it was possible for patients to shift from one group to another as a result of specific changes from day to day testing. This idea was supported by Daly, Siekert and Burke (1959) whose observations did not suggest a simple relationship between light sensitivity and the occurrence or severity of seizures.

Analysis of individual differences in the electro-retinogram (ERG), visual and somatosensory evoked potentials, (VEP, SEP) in photosensitives led Broughton, Meier-Ewert and Ebe (1969) to suggest a patient differentiation based on the inter-subject variabilities apparently acting at all levels of the primary, non-specific visual system. Doose, Giesler

and Völzke (1969b) based their classification on clinical seizures, again dividing patients into 3 groups :-

(i) Photogenic epilepsy - cerebral seizures only occur under the influence of light stimulation e.g. television epilepsy and self-induced epilepsy;

(ii) Epilepsy in which both photogenic and spontaneous seizures occur;

(iii) Photosensitive epilepsy - seizures occur independently of any detectable light stimuli; a photoconvulsive response (PCR) only being revealed by the EEG. In some patients, however, clinical seizures can be triggered by very intense light stimulation under laboratory conditions.

This classification is slightly confusing, due to the terminology 'photogenic' which is commonly used in photography (Jeavons and Harding 1975). A comprehensive classification was developed by these latter authors based on clinical and EEG responses. The percentages refer to the proportion in each group from 454 patients :-

Group A Fits only occurred with television (35%);

Group B Fits have occurred while watching television and also spontaneously at times when there was no evidence of flickering light as a precipitant (22%);

Group C Fits occurred with television and also when the patient was exposed to flickering and bright light from other everyday sources. No fits occurred spontaneously. (5%);

Group D Fits have occurred with television, flicker from other sources and also spontaneously. (4%);

Group E Fits were evoked by flickering or bright lights but not by television. Spontaneous fits have occurred. (7%);

Group F Spontaneous fits only occur. There is no evidence of clinical photosensitivity. All patients show spike and wave in the EEG during IPS. (27%).

It is possible for a patient to move into another group if a new precipitant becomes incidental in evoking seizures. As a result of this classification the authors found that 66% of photosensitives were television-sensitive. For analytical purposes, it was possible to recombine the 3 groups into 3 major divisions :-

Group 1 (A + C) - Flicker sensitive (40%);

Group II (B + D + E) - Flicker sensitive and spontaneous attacks (33%);

Group III (F) Spontaneous attacks only, photosensitive during laboratory IPS (27%).

1.5. Seizure Type.

Tonic-clonic convulsions are consistently quoted as the most usual type of seizure in photosensitive epilepsy (Melsen 1959; Gastaut et al. 1960; Charlton and Hoefer 1964 1964; Wadlington and Riley 1965: Hishikawa, Yamamoto, Furuya, Yamada, Miyazaki and Kaneko 1967; Doose et al. 1969b; Lopez 1973). Generalised seizures whether tonic-clonic, myoclonic jerks, or absences are predictable as bilateral 3 c.p.s. spike and wave abnormalities often occur during IPS (Jeavons and Harding 1975). These authors found that 67% of their photosensitive patients suffered from tonic-clonic fits or loss of consciousness, particularly those clinically purely flicker-sensitive (Group 1). Minor absences occurred in 13% of patients, mostly those with spontaneous fits and those showing only laboratory photosensitivity, but rarely those patients in Group 1. Myoclonic jerks only, were found in 4% of patients, the highest incidence being found in the clinically mixed group (Group II), in that the important factor was the tendency to spontaneous fits. Partial seizures with focal clonic convulsions or psychomotor attacks only occurred in 2.4% of patients. The most interesting aspect in this group was the subjective awareness that patients underwent just before the attack occurred. Similar sensations, e.g. nausea , unpleasant taste, giddiness, occurred at times when viewing television, in sunlight and during IPS. A few patients with spontaneous tonic-clonic seizures also experienced 'peculiar feelings' under the same conditions. Other photosensitives (14.3%) had two or more seizures; the most common combination being tonic-clonic and minor seizures, followed by myoclonic fits and tonic-clonic convulsions.

An accurate diagnosis of epilepsy depends on detailed study of the patients' clinical history, i.e. type of seizure, EEG during seizures, EEG between seizures, anatomical substrate, etiology and age of onset (Gastaut, Caveness, Landolt, Lorentz de Haas, McNaughton, Magnus, Merlis, Pond, Radermecker and Storm van Leeuwen 1964). Epileptic attacks involve the paroxysmal discharge of electrical activity, and it is the site of origin of this abnormal discharge that provides a general division into primary sub-cortical and cortical epilepsy. The former is also known as centrencephalic, constitutional or idiopathic, as the paroxysmal discharges are believed to arise from the brain stem and there is a relatively greater possibility of inherited disposition, otherwise the cause is largely unknown (Roberts 1974). Cortical epilepsy is commonly known as symptomatic, inferring structural damage to the brain. However, even a discrete focus of paroxysmal activity may provoke secondary generalised seizures. Some authorities believe that all epilepsy has a focal ictus (Alström 1950).

Photic stimulation appeared to be a more effective activator in idiopathic epilepsy than in symptomatic (Melsen 1959). The most common finding was 'irregular bilateral paroxysmal activity' occurring in 7% of symptomatic and 25% of idiopathic epileptics. Watson and Marcus (1962) found a similar incidence of photically evoked EEG abnormality in symptomatic epileptics (4.5%) as in normal, unaffected adults (5%) and a large group of patients without seizures (6.8%). Doose et al. (1969b) stated that, although a PCR was more common in the centrencephalic epilepsies, it could also be found in febrile convulsions, psychomotor seizures and other forms of epilepsy.

1.6. Aetiology of Photosensitivity.

An understanding of any epileptic condition depends on the incidence of epilepsy in various age groups of the general population; the incidence of seizures amongst blood relatives, particularly in relation to the possible genetic and procured factors; the incidence of seizures in relatives in which the hereditary factor is known, i.e. identical twins; incidence of asymptomatic EEG abnormalities in epileptics, in patients' relatives; and in the general population (Lennox 1947).

1.6.1. Inheritance.

It has long been realised that the study of cortical activity might clarify the problem of inheritance in epilepsy (Lennox, Gibbs and Gibbs 1939). The idea arose from the individuality of a person's EEG and the similarity of normal and abnormal recordings in identical twins. Early studies by these authors showed that abnormal EEG rhythms were not only present during seizures but also during the intervening periods.

Twin studies are of prime importance in heritability studies. Idiopathic epilepsies overall have shown a high concordance (84%) in monozygotic twins (MZ) but a relatively low concordance (10%) in dizygotic twins (DZ) (Lennox 1951). A similar study in symptomatic patients showed concordance figures of 17% and 8% respectively. Daly and Bickford (1954) were the first to report case studies of a pair of female, photosensitive MZ twins aged 42 years. Onset, type of seizures and subjective sensations were identical. Both showed similar spike and wave discharge from 5 f.p.s., although one twin had more paroxysms initiated by spiking. Also, both twins suffered with migraine and, although there was no

definite family history of convulsions, 'sick headaches' were prevalent on the maternal side, a younger sister had syncope and a maternal cousin had 'little blinking spells'. Davidson and Watson (1956) studied four pairs of MZ twins. They also found light-sensitivity in 62% of asymptomatic relatives and in some fits occurred for the first time during IPS. None of the patients or their relatives had focal lesions of the nervous system. The authors suggested that light sensitivity is a manifestation of a predisposition to diffuse neuronal disease.

Despite the opinion that heredity plays an important part in epilepsy, only 1 in 5 persons are able to name any relative similarly affected (Lennox et al. 1939). The predisposition to seizures may lie dormant, then suddenly appear as a result of trauma or other environmental or genetical factors. EEG recording techniques, viz. hyperventilation, IPS, and sleep studies may show this predisposition. A light-sensitive family was described by Daly et al. (1959). Of 4 children, 3 siblings were photosensitive. One child had previously suffered febrile convulsions but, of the other 2 non-epileptic children, the eldest was the most photosensitive and showed myoclonic jerks for the first time during IPS. The authors suggested that photosensitivity might be the result of neuronal disease which need not be associated with convulsions but might also arise from a defect in the subcortical systems, or even at a cortical level through biochemical or autonomic distrubances, possibly under hereditary influences.

Human traits are the result of interplay between the environment and genetic factors. Metrakos and Metrakos (1960)

proposed the existence of three types of epistatic genes; threshold genes, cerebral disease genes and epilepsy genes. These supposedly influence the amount of stimulation required to precipitate an individual's innate capacity to convulse. Variation in penetrance, expressivity, and chronicity could all combine making the divison between affected and unaffected persons obscure. A study of 195 parents and 223 siblings of centrencephalic epileptics showed that hyperventilation and IPS induced typical and atypical 3 c.p.s. spike and wave in 8% of parents and 37% of siblings (Metrakos and Metrakos 1961). They proposed that an autosomal dominant gene was involved in the inheritance of this 'centrencephalic EEG' but was unusual in showing variability in age of onset and termination of its expression. Approximately 45% of the siblings with 3 c.p.s. spike and wave were between 4.5-16.5 years of age, within which an optimum age probably existed where the dominant gene became fully penetrant.

Schwartz (1962) reported a family of 4 photosensitive siblings, 2 of whom were clinically flicker-sensitive; the other 2 asymptomatic children showed occipital spikes or a PCR. The female non-epileptic sibling also experienced unpleasant sensations with bright and flickering lights and the father reported a history of similar subjective feelings. His EEG, however, only showed episodic theta with occasional sharp waves and there was no significant activation during IPS. A high incidence of 'photogenic cerebral electrical abnormalities' was found in 146 asymptomatic relatives of 60 epileptics, i.e. 50% of mothers, 17% of fathers, 45% of siblings and 32% of offspring (Watson and Marcus 1962). However, 5 types of EEG abnormality

were included in their classification, only one type clearly being a PCR. The authors did note, however, that IPS evoked generalised convulsions, myoclonus and absences in a few relatives with no history of seizures. Further evidence of familial photosensitivity was reported by Haneke (1963) and Brausch and Ferguson (1965) where the asymptomatic relatives obviously had higher thresholds than the actual photosensitive epileptics.

Photosensitivity was found to be markedly age linked with the highest incidence among the 5-8 yearold siblings of photosensitive patients (Doose et al. 1969b). The disposition to seizures was also more frequently seen in female members of a family, particularly on the maternal side. These authors also found PCRs in clinically healthy controls and numerous non-convulsive disorders, viz. migraine, behaviour disturbances, and concluded that photosensitivity was a widely distributed symptom of dispositional susceptibility to convulsions of the centrencephalic type. The role of heredity was thought to most probably be influencing the functional instability of certain reticulo- cortical structures and, though the mode of transmission was uncertain, it was possible that other genetic factors were important in triggering seizures. Scollo-Lavizzari (1971) following up non-epileptic patients with migraine, head injury and behaviour disorders, all originally having shown spike and wave during IPS, found that within 7 years, only 1.4% had developed epileptic seizures and now only 37% showed asymptomatic epileptiform discharges. He postulated that sensitivity to IPS was the expression of gene-controlled neuronal excitability.

The largest family with definite inheritance of photosensitivity is one of 11 surviving siblings and 4 second generation children (Herrick 1973; Herrick, Jeavons and Harding 1975). Three children had experienced a fit whilst watching television; all had normal resting EEGs but IPS evoked spike and wave discharges. One of these siblings had later married an epileptic man and had a child which, at 3 years of age, was having febrile convulsions. This daughter had another clinically normal child, aged 2 years, by another man. Both her sons had normal EEGs and showed no signs of photosensitivity. Three other boys in the family had no history of fits. Their basic EEGs were normal but one sibling (17 years) had occipital spikes in his visual evoked potential (VEP) and another(18 years) had occipital slow waves during IPS. The eldest male sibling had a completely normal EEG even during IPS. He had married a woman whose mother may have had fits and who herself, though clinically normal, showed occipital spikes during IPS. Their 2 children, one being the step-child of the eldest son, had normal EEGs. The other 5 siblings in the family were asymptomatic females. All had normal basic EEGs but IPS evoked spike and wave in 3 of them. One other had occipital spikes in the VEP. The mother, aged 48, had a normal basic EEG but occipital abnormality occurred during IPS.

The evidence therefore from surveys and anecdotal reports suggests that genetic transmission of photosensitivity is complex but is probably governed by autosomal genes that interact between themselves and other genetic factors, thus influencing the severity of the condition. Consequently, varying degrees of photosensitivity are seen both in the

clinical response and EEG pattern during photic stimulation.

1.6.2. Age.

The relative frequency of different types of epilepsy is a function of age in that generalised epilepsy is more common under the age of 15 years than partial epilepsy (Gastaut, Gastaut, Gonçalves e Silva and Fernandez- Sanchez 1975). Herrlin (1954) found that a variety of abnormal responses to IPS were twice as frequent in children with definite or suspected epilepsy aged between 5 - 15 years than in children under 5 years of age. The younger children also appeared to be untroubled by IPS, whereas older children experienced feelings of discomfort even in the absence of a 'pathological response'. He stated that sensitivity to photic stimulation increased with increasing age with an upper limit of 15 years in his series. Melsen (1959) however, disagreed with these findings in that he found photosensitivity, in idiopathic and symptomatic epileptics, to decrease with increasing age. The incidence of spike and wave, slow waves, spikes or sharp wave was 22.4% up to 5 years of age, 15.2% between 6 - 15 years, and 9.5% in the 16-60 year age group. However, in all age groups, the idiopathic epileptics greatly outweighed the symptomatic patients. Discrepancy between these two authors may have arisen due to the proportion of seizure types studied. Generalised seizures constituted 85% of Herrlin's and 64% of Melsen's epileptic sample. Also, there was variability in the type of responses considered abnormal. Walter et al. (1946) found that in children up to 14 years of age, occipital rhythms evoked by IPS were relatively large at low flash rates. Corbin, Pennel and Bickford (1955) observed that in 1-10 year olds,

the most marked changes in EEG frequency occurred in the parieto-occipital region and that the abnormal rate of specific discharge was higher in children than in adults. Sharp wave discharges in younger children could disappear spontaneously, indicating a slow cortical maturation towards stability and less pathological significance of these dischages in young children. Brandt et al. (1961) reached a similar conclusion from studying the effects of IPS on 120 non-epileptic children. Marcus and Watson (1962) found that less than 1% of patients without a history of seizures, under 6 years of age, showed 'photogenic cerebral electrical abnormalities'. As previously mentioned, this description covered a wide range of responses to IPS. However, at 6-10 years the incidence increased to 15%, to 17.5% in the 11-15 year age group, and between 21-60 years 'abnormalities' were observed in 7.4%. They also found marked photosensitivity with associated myoclonic jerks, absences or generalised convulsions in a select group of epileptics where the median age of seizure onset was 8 years.

Gastaut et al.(1960; 1961) reported that in a group of photosensitive patients the average age was 19.2 years; 53% were aged between 0-10 years, 18% 11-20 years, 23% 21-30 years and 6% 31-40 years. In the same study the average age of 25 patients with 'television epilepsy' was 15.2 years. Charlton and Hoefer (1964) found that the modal age for onset of 'television epilepsy' in their series was 8-14 years and suggested a hypersensitivity to photic stimulation existed particularly in older children, and that a subsequent reduction in the number of fits was partly due to diminished photosensitivity with increasing age. Wadlington and Riley (1965) noted that

the majority of photosensitive epileptics were clinically referred during childhood.

The youngest reported child to show abnormal discharges during IPS was aged 2 years 3 months (Capron 1966). However, this child had gross cerebral lesions and the author found that the incidence of photically evoked abnormality was rare before the age of 5 years; onset mainly occurring between 5-15 years. Richter (1960) described the case history of a male, aged 52 years, with tonic-clonic seizures precipitated by television and laboratory photosensitivity. He had no family history of epilepsy.

Photosensitivity is strongly age dependent (Gerken, Doose, Völzke, Völz and Hein-Völpel 1968). In siblings of photosensitive epileptics, the highest proportion of photically induced abnormalities occurred in the age range 11-13 years (36.7%). When only generalised spike and wave was considered, an incidence of 19.4% was found between 1-15 years for siblings, and only 3.4% for age matched controls. There was no difference in the relative occurrence of occipital biphasic waves. The photosensitive epilepsy described by Doose and his colleagues refers to patients exhibiting photosensitivity during IPS, but with only a clinical history of spontaneous seizures. In a group of these patients, 67% were found to have suffered their first seizure before the age of 6 years and, therefore, before the age of maximum penetrance of photosensitivity. (Doose et al. 1969b). However, 'photogenic epilepsy' i.e. clinical flicker-sensitivity, predominated in children between 8-15 years, almost exclusively within the age range of maximum penetrance. The siblings of photosensitivies showed a 40% occurrence of PCRs in those

aged between 5 - 8 years, 26.4% between 9-15 years and 34.5% between 13 - 16 years. However, a PCR was rare in parents, aunts, uncles and grandparents. The highest incidence in these relatives was 8% of parents, which was similar to the frequency of PCRs found in normal control subjects (Doose, Gerken, Hein-Völpel and Völzke 1969a).

Of 454 cases reported by Jeavons and Harding (1975), the youngest child in which IPS evoked a PCR was aged 2 years 5 months. The overall range of ages was 2 - 58 years, with a mode of onset at 12 years and a mean of 13.7 years, suggesting that puberty was strongly linked with the onset of photosensitivity. In 76% of all cases onset occurred between the ages of 8 - 19 years. The authors described the case histories of 2 siblings. The female, with a PCR at 6 years, subsequently had a fit while viewing television at the age of 10 years. Her brother exhibited a PCR at 3 years but a fit occurred later at 8 years of age.

1.6.3. Sex.

Herrlin (1954) appears to be the first author to report the preponderance of females in a clearly epileptic and suspected epileptic population showing a pathological response to photic stimulation. Melsen (1959) agreed with these findings but stated that the incressed frequency of photic activation was only found in the idiopathic epilepsies and particularly in patients with tonic-clonic seizures. Watson and Marcus (1962) found that from 11-60 years of age three times as many females than males showed 'photogenic cerebral abnormalities'. No sex differences occurred after 60 years. However, Bower (1963) and Charlton and Hoefer (1964) reported no undue sex preponderance in their studies of 'television epilepsy'. This

may have been due to the small sample sizes of 14 and 9 patients respectively. Haneke (1963) described the case of a female patient with 'photogenic seizures' and a family history of photosensitivity in female relatives on the maternal side. Disposition to seizures in the photosensitive epilepsies was found to be nearly twice as frequent among patients' female relatives than male relatives, particularly on the maternal side, (Doose et al. 1969a, b). The authors found that although in all groups females outweighed the males, female predominance was marked within the puberty age range. They proposed, therefore, that hormonal factors are only especially relevant around puberty,

Not all studies on photosensitivity quote the relative proportions of males to females. A survey of the literature where statistics are available showed that overall, 64% of patients examined were female (Panayiotopoulos 1972). It may be possible that a more vigorous response to IPS occurs in females. Procopis and Jameson (1974) found that more females than males were equally sensitive during binocular and monocular IPS and relatively fewer females insensitive to monocular stimulation.

Wadlington and Riley (1965) were not aware of any other type of epilepsy, except typical absences, that had a definite predominance of females. In the general population, males are predominant and also in other forms of epilepsies, viz. infantile spasms, febrile convulsions and, to a lesser extent, psychomotor epilepsy, tonic-clonic convulsions and focal fits. On the other hand Jeavons and Harding (1975) found that in photosensitive epilepsy 63% were female and 37% male, regardless of type of fit. Females predominated in all types of

patients showing photically evoked EEG abnormality, in all patients whom IPS induced myoclonic jerks and absences (77%), and in all patients with non-photosensitive typical absences. The highest proportion of females occurred in patients whose light-induced fits were either absences or myoclonic jerks. When considering clinical group classification (see Section 1.4), the high incidence of these types of seizures in Groups E and F were therefore thought to be directly related to the predominance of females in these groups. The only group of photosensitives showing a similar sex ratio to other non-photosensitive epileptics was those 'impulsively attracted' to television.

1.7. Photostimulators.

The first photostimulator was an opal glass bowl behind which was a sectored wheel, rotated by a gramophone motor, and lit by a headlamp bulb (Adrian and Matthews 1934). This primitive model was able to produce flicker rates up to 25 f.p.s.. The first electronic stroboscope was introduced by Walter et al. (1946). They stressed the need for a device that could produce fast flash rates without variation in intensity and duration of each flash.

An early belief was that sectored-light evoked different EEG responses than stroboscopic-light (Daly and Bickford 1951). Ulett and Johnson (1958) employed sectored-light, using a disk-episcotister constructed in their laboratory, that produced flash rates from 3 - 33 f.p.s.. Nowadays, many types of electronic stimulators have been developed for clinical use. Most are gas-discharge lamps producing a blue-white flash of 10-30 μsec. duration, although durations of up to 100 μsec. have been reported (Hishikawa et al. 1967). Some of these stroboscopes give flicker rates up to 50 f.p.s., others to 100 f.p.s.; some can deliver paired flashes with varying intervals between each flash; and in some cases it is possible to trigger the stroboscope from the patient's EEG (Jeavons and Harding 1975). This leads to great variability in experimental technique. Some photostimulators possess diffusing screens or metal protective grids in front of the lamp which may vary in size. The intensity of the light source tends to fall away at the periphery also leading to discrepancies as regards the amount of visual field stimulated.

It is notable in the literature that authors measure intensity in differing units, and there is lack of standardisation in that either luminance or illuminance units may be reported. Luminance, or brightness, refers to the flux radiated from a unit area of a large light source, i.e. the luminous intensity per unit area, projected in the viewing direction, and is measured in candelas (lumens per steradian), e.g. nits (candelas/square metre), lamberts ($\frac{1}{\pi}$ candelas/square centimetre). Illuminance, or illumination, refers to the flux falling on a unit area of a surface, i.e. the incident flux per unit area, and is measured in lumens, e.g. phot (lumens/square centimetre), lux or metre-candles (lumens/square metre), foot-candles (lumens/square foot).

Some photostimulators calibrate intensity in arbitrary units of specific energy, e.g. Grass intensity 1-16, Kaiser 0.1 - 0.6 joules. It is, however, possible to measure the precise output (Jeavons et al. 1972b). The mean luminance of the stimulator, placed at the usual viewing distance, can be measured using an S.E.I. photometer at a frequency of about 20 f.p.s. at the various intensity settings. The results obtained in foot-lamberts can be converted to nits, which are appropriate units for pulses of short duration, by multiplying the former by a conversion factor. However, intensity measurements are slightly inaccurate for, although intensity versus frequency is essentially constant, slight attenuation occurs with very high intensities at fast flash rates.

1.8. Frequency.

Most photostimulators deliver flash rates between 1-50 f.p.s. In the literature, rates from 1 - 85 f.p.s. have been reported (Jeavons 1969). However, few authors have tested the response to IPS at rates above 30 f.p.s. (Ulett and Johnson 1958; Gastaut et al. 1961; Pallis and Louis 1961; Pantelakis et al. 1962; Forster and Campos 1964; Jeavons, Harding and Bower 1966; Jeavons and Harding 1975). The most effective frequencies for evoking paroxysmal EEG discharge have been quoted within 6 - 30 f.p.s., most authors finding a peak response between 10 - 20 f.p.s. (Carterette and Symmes 1952; Bickford et al. 1953; Marshall, Walker and Livingston 1953; Herrlin 1954; Troupin 1966; Meier-Ewert and Broughton 1967; Bickford and Klass 1969; Jeavons and Harding 1970; Chorley 1972; Procopis and Jameson 1974). Several authors have suggested 15-16 f.p.s. to be the optimum screening flash rate (Hutchinson et al. 1958; Gastaut et al. 1960; Hughes 1960). Jeavons and Harding (1975) found that the highest proportion of patients exhibiting a PCR was 89% at 16 f.p.s., with 96% of patients reacting between 15-20 f.p.s.. They suggested that screening at 25 and 50 f.p.s. was also necessary, as this covered the television flicker frequencies in European countries. At fast flash rates, 49% of patients were sensitive to 50 f.p.s. and 15% to 60 f.p.s. This contradicted the previous findings of Richter (1960), Gastaut et al. (1961) and Pallis and Louis (1961) who did not find convulsive responses above 40 - 50 f.p.s..

In 1971 the Greater London Council banned the use of flicker rates above 8 f.p.s. in discotheques. However, Jeavons and Harding (1975) recommended a ban on flash rates

above 5 f.p.s. as 42% of patients were sensitive to 8 f.p.s. and even a quarter of their large photosensitive population were still sensitive at 6 f.p.s.. A few authors have observed spike and wave abnormalities and even seizures in very highly sensitive patients to single flashes (Bickford et al 1953; Mawdsley 1961; Troupin 1966; Jeavons and Harding 1975).

A variation in frequency response was found according to age (Melsen 1959). Adults (16 - 60 years) showed peak abnormality at 12 - 14 f.p.s., whereas in children (up to 15 years) optimum frequencies were 6 - 18 f.p.s. but with greater dispersion of response. The lowest frequencies, 4-8 f.p.s., were relatively more effective in the younger children. Single flashes and low flash rates up to 4 f.p.s. produce visual evoked potentials (Jeavons 1969). Such isolated slow wave responses tend to be of increased amplitude in children (Brandt et al. 1961). Therefore, when authors combine a true PCR with a variety of other photically evoked responses and classify them as abnormal, e.g. 'other bilateral discharges of low frequency and high amplitude contrasting with the background rhythm' (Melsen 1959) and 'photogenic cerebral abnormalities' including 'progressive recruitment of evoked responses' (Watson and Marcus 1962); inaccurate conclusions as to the incidence of paroxysmal discharge in children at low flash rates could easily arise.

A rare technique in IPS has been the use of double flashes (Capron 1966; Meier-Ewert and Broughton 1967). Richter (1960), presenting double flashes at 6 and 8 f.p.s., provoked generalised spike and wave discharges, and double flashes at 12 f.p.s. evoked a tonic-clonic fit in one patient (Haneke 1963). It should be noted that double flashes

at 6-12 f.p.s. are in effect producing the particularly evocative frequencies of 12-24 f.p.s..

Triggering IPS from a patient's EEG was first reported by Walter et al. (1946). An electronic trigger circuit was employed to synchronise flashes either with the unfiltered EEG activity or with any selected component using automatic analysis. Melsen (1959) used this technique to present IPS in response to negative and then positive rhythm components. He found an increased response occurred in adults with stimulation of positive components. However, although this technique may increase the incidence of abnormal EEG responses in patients and normal subjects, its use in clinical electroencephalography is limited, as results cannot be compared between patients and within the same patient on different occasions (Jeavons 1969).

Many authors deliver flash rates one at a time when testing photosensitivity. However, some have used continually changing flash rates by rapidly altering the frequency or by slow 'sweeping' changes from 1 f.p.s. or very low frequencies up to 20 - 30 f.p.s. and vice versa (Hughes 1960; Herrlin 1954; Doose et al. 1969b). This, however, has resulted in prolonged photic stimulation for up to around 30 seconds which may present added complications of hypersensitivity or habituation. Jeavons (1969) states that it is preferable to expose patients to one flash rate at a time.

1.9. Duration of IPS.

Details are not always available in the literature as regards the duration of continuous IPS. However, when reported it is evident that duration is a diverse variable with continuous exposure periods ranging from 2 seconds (Jeavons et al. 1966) up to 20 minutes (Herrlin 1954). Duration of IPS has depended on the type of EEG and clinical response under investigation, and on the characteristics of the sample under study, viz. normal controls, epileptics, photosensitive patients. Studies have involved continuous IPS intervals of 2-3 minutes (Lloyd-Smith and Henderson 1951), 3-4 seconds (Hutchinson et al. 1958), 40 seconds (Ulett and Johnson 1958), 35 seconds (Melsen 1959), 10-15 seconds (Hughes 1960), up to 5 minutes (Mawdsley 1961), 10 seconds (Wadlington and Riley 1965), and 30 seconds (Doose et al. 1969a).

Some authors developed an IPS regime using fixed time intervals between each train of flashes. Carterette and Symmes (1952) presented randomly ordered flash rates for 10 seconds followed by a 10 second rest period; Hughes(1960) used a screening frequency of 16 f.p.s. for 2 seconds on and 1 second off; Pantelakis et al. (1962) presented IPS for 10 seconds, incorporating eyes-open, eye closure and eyes-closed, with a 10-second interval between each test frequency; Johnson (1963) induced hypnotic effects in pilots with electronically controlled IPS of 30 seconds on and 30 seconds off; Forster and Campos (1964) randomly varied the interflash period between 30 seconds and 3 minutes; Procopis and Jameson(1974) presented flicker for 4 seconds every 10-15 seconds.

The importance of the inter-stimulus rest period was first mentioned by Brausch and Ferguson (1965). When successive trains of flashes were given within intervals of 3 seconds, a diminution occurred in the PCR. The latency of the response, however, showed no significant change. Conversely, Troupin (1966) noted that a step-like buildup in EEG activation was related to increases in the length of stimulation and, in this way, it was possible to broaden the span of effective frequencies. The author suggested leaving at least 10 seconds between trains of flashes to allow cerebral activity to return to baseline. Capron (1966) observed habituation to white light after testing with coloured filters but, nevertheless, by repeating a series of flashes even at the same frequency, found summation of paroxysmal activity as a result of increased disorganisation.

The extremely high incidence of EEG abnormalities in non-epileptic children (25.8%) reported by Brandt et al. (1961) probably resulted from their technique of continuous IPS for 6 minutes close to the eyes. Prolonged photic stimulation in photosensitive individuals will eventually provoke fits. Although exposing subjects with up to 20 minutes of IPS, in some cases Herrlin (1954) varied the duration in epileptic children and interrupted the flash when marked EEG paroxysm indicated an imminent convulsion. Similarly, Melsen (1959) ceased IPS at the signs of an approaching seizure. Bablouzian, Neurath, Sament and Watson (1969) recorded myoclonic phenomena in photosensitive epileptics during IPS at 15 f.p.s. presented at 1 - 2 second intervals. Continuous flicker evoked generalised convulsions. Standardisation of IPS has therefore been recommended in order to reduce the potential hazards of photic

stimulation and that frequencies should be tested one at a time for 2 seconds, preferably by means of an electronic trigger with an over-ride so that IPS can be immediately stopped at the signs of polyspikes and myoclonic jerking (Jeavons and Harding 1975).

1.10. Intensity and Diffusion.

Adrian and Matthews (1934) first noted the effect of light intensity on brain rhythms while investigating photic driving. Variation in photosensitive thresholds was later reported by Marshall et al. (1953). Although no details were given as to the levels of intensity used, they found that as brightness increased the sensitivity range widened. This finding was supported by Troupin (1966). Photically evoked responses in fact strongly depend on the relative brightness of the light source in comparison to the background illumination and to the area of visual field stimulated (Jeavons and Harding 1975). On this basis of differential light intensity 'anti-flicker spectacles' were devised by Harding, Drasdo, Kabrisky and Jeavons (1969), and 'conditioning therapy' investigated by Forster, Ptacek, Peterson, Chun, Bengzon and Campos (1964).

Comparison of intensity levels in the literature is difficult, as units differ and sometimes authors have varied intensity according to different flash rates, e.g. 200,000 foot-candles (f.c.) (Carterette and Symmes 1952); 400,000 f.c. (Bickford, Sem-Jacobsen, White and Daly 1952); 300,000 f.c. (Bickford et al. 1953); 88,000 f.c.(Herrlin 1954); 100 f.c. at the periphery and 200 f.c. centrally at the light-source (Ulett and Johnson 1958); 10,000 - 330,000 f.c. depending on flash rate (Melsen 1959); 0.25 - 1 megalux with higher intensities at low flash rates (Brandt et al. 1961); 1,000,000 f.c. (Johnson 1963); 0.3 joules of an Alvar stroboscope (Capron 1966); 0.45 joules with a peak intensity of 150.10^4 lux (Hishikawa et al. 1967); Grass intensity 16 (920,000 f.c.) for PMR investigation (Meier-Ewert and

Broughton 1967); Grass intensity 4 (0.4 x 10^6 lamberts) and Grass intensity 16 (1.6 x 10^6 lamberts) for evoked potential analysis (Bablouzian et al. 1969); Knott intensity II (Doose et al. 1969a).

Melsen (1959) found that a sudden increase in light intensity after 25 seconds of continuous IPS produced relatively greater paroxysmal response in females than in males, although he concluded that flicker played a greater role than light intensity. Pantelakis et al. (1962) found two distinct groups as regards sensitivity to intensity. By placing sheets of white paper over the plain glass screen of a stroboscope, they obtained intensities of 35%, 15% and 11% of the original level. Half the patients showed spike and wave at 11%, the other half had no PCRs even at the 35% level. In 1 patient, mild activity occurred over the whole frequency range with the undimmed lamp but with the sheets of paper, producing 11% of this intensity, definite PCRs occurred. It is notable that this action not only altered the intensity of the light but also increased diffusion.

Photostimulators may possess a ground, frosted or patterned glass screen, thus varying the amount of diffused light. Carterette and Symmes (1952) placed diffusing goggles on their patients to prevent structuring and discontinuities in the visual field. Melsen (1959) employed a diffusing screen of 16 cms.. The increased effectiveness of a diffused light source was reported by Brausch and Ferguson (1965). They stated that although diffusion decreased the illuminance at any given point and thereby diminished the 'brightness' of its corresponding retinal image, more of the visual field became stimulated and thereby reduced the photoconvulsive

threshold. The authors did not propose a simple, direct relationship between the efficacy of diffuse light and the area of visual field stimulation. They implicated the lateral geniculate nuclei, in that diffuse retinal illumination appeared to augment geniculate-induced cortical potentials and that a background of diffused light was necessary for the maintenance of specific cortical responses to geniculate stimuli. Jeavons and Harding (1975) found a diffusing screen was 1.4 - 2.9 times more effective than plain glass and evoked more PCRs at lower intensities. Together with Troupin (1966), these authors recommended the routine use of diffusing screen during IPS, with a small fixation point at the centre to maintain the subject's attention.

As previously mentioned, intensity can be measured in standardised units, despite the type of photostimulator (see Section 1.7). Jeavons and Harding (1975) proposed that the luminance unit of the nit (candela/sq.m.) is applicable when determining the degree of photosensitivity of an individual. Units of retinal illumination were suggested as being more appropriate in analytical studies of CNS responses with controlled pupil size.

1.11. Background Illumination.

The effectiveness of light intensity is dependent upon its relative intensity against the background illumination. Unfortunately, background illumination has been measured by few authors. A level of 1 metrelux was reported by Meier-Ewert and Broughton (1967) and 1 lambert (actually a unit of luminance and not illumination) by Bablouzian et al. (1969). Many authors simply report using a low level of ambient light, or a dimly lit room (Carterette and Symmes 1952; Herrlin 1954) or a darkened room (Hughes 1960; Forster and Campos 1964; Doose et al. 1969a). Some studies have been conducted under 'normal background ambient illumination' (Gastaut et al. 1961) or daylight (Capron 1966). Jeavons and Harding (1975) recommended that the background illumination should be a dimmed artificial light. Although brightness enhancement of a flickering light increases in dark surroundings, such conditions do not allow clear observation of the patient's direction of gaze or any behavioural response to IPS.

1.12. Distance of the Lamp.

The distance that the lamp is placed away from the subject's eyes is another important variable. Distances have varied from 2.5 cms. (Wadlington and Riley 1965) to 3 metres (Gastaut et al. 1961). Most reports quote distances ranging from 10 - 30 cms. away from the outer canthus of the eye or the bridge of the nose (Herrlin 1954; Ulett and Johnson 1958; Melsen 1959; Hughes 1960; Brandt et al. 1961; Capron 1966; Meier-Ewert and Broughton 1967; Bablouzian et al. 1969; Doose et al. 1969a; Jeavons 1969; Procopis and Jameson 1974). A few authors have used distances greater than 30 cms., e.g. 45 cms. (Bickford et al. 1952), 1 metre (Forster and Campos 1964), up to 112.5 cms. (Pallis and Louis 1961).

Obviously, differences in the degree of photosensitivity between individuals, together with the variation in lamp size, and whether the patient's eyes are open or closed, will also affect the type of response. However, the closer the photostimulator is to the eyes, the greater the area of retinal stimulation. Procopis and Jameson (1974) noted that during monocular stimulation the light had to be brought half the distance away from the patients' eyes in order to evoke EEG abnormalities similar to those seen during binocular stimulation. During routine testing placing the stroboscope 30 cms. away from the eyes not only allows observation of the patient's direction of gaze but also stimulates a large proportion of the visual field, e.g. at this distance a Grass stroboscope subtends a 24.5° visual angle (Jeavons and Harding 1975).

1.13. Colour.

The effect of coloured light on photically evoked abnormalities has been investigated by several authors, many of whom came to the conclusion that red light was particularly effective in evoking convulsions as well as spike and wave discharge (Carterette and Symmes 1952; Courjon 1955; Pantelakis et al. 1962; Brausch and Ferguson 1965; Capron 1966). Bickford et al. (1953) although also finding the red end of the spectrum relatively more provocative than other colours, induced seizures with green and blue light. The wearing of tinted spectacles or contact lenses was therefore proposed for the clinical management of patients, depending on their colour sensitivity, viz. glasses that totally eliminated red light (Carterette and Symmes 1952; Marshall et al. 1953; Courjon 1955; Brausch and Ferguson 1965; Bickford and Klass 1969).

Difficulties arise when interpreting the effects of colour reported in the literature. Dense filters have usually been used which also reduce the intensity of light (Troupin 1966). Most studies employed Kodak Wratten filters and when details are given, the specifications show differences in transmission values. Also discrepancy may have arisen from the use of different IPS frequencies, criteria of the abnormal response and failure to differentiate between eyes-open, eyes-closed and eye-closure (Jeavons and Harding 1975).

Pantelakis et al. (1962) tested television sensitive children with red, green and blue IPS which were 7%, 7% and 12% respectively of the original light intensity. The patients previously sensitive to low intensity light were also sensitive to coloured IPS with eyes open, in particular

red light. In patients previously sensitive to high intensity stimulation, no discharges occurred with coloured light, However, in all patients during eyes-closed IPS, red light evoked PCRs whereas blue and green light were ineffective. Others had already commented on marked EEG activation with red light during eyes-closed IPS and attributed it to the red-filtering effect of the eyelids (Carterette and Symmes 1952; Bickford et al. 1953). However, Brausch and Ferguson (1965) did not regard the 'eyelid red-filter' theory as the full explanation. They observed that eye-closure could enhance the PCR and proposed that the eyelids were acting as a diffuser and so causing a greater area of retina to become stimulated.

Troupin (1966) attempted to control intensity, diffusion and attention variables. He reported that with eyes-closed, white light evoked most EEG activation, followed by eyes-open. Both conditions evoked PCRs more often than blue, green or red filters, although the frequency plot for red stimulation followed the same trend as for white light with eyes-closed. This author believed that cerebral mechanisms played a greater part than the red-filter effect of the eyelids. However it should be noted, in this study eyes-closed probably immediately followed eye-closure during continuous IPS, and that eye-closure is particularly effective in evoking PCRs (Jeavons 1966). Capron (1966) found that of 66 patients, 41 were more sensitive to red light than green or blue, and particularly those with myoclonic epilepsy in comparison to those with absence or other forms of seizure. During the 20 seconds of continuous IPS, eyes-open constituted no more than 5 seconds. Placing a red filter in front of open eyes did not increase the discharges and

electroretinographs (ERG) showed that the intensity of the red light was altered very little when the eyes were closed, whereas blue, green or neutral filters reduced the ERG considerably.

Jeavons and Harding (1975) matched colour filters for transmission equated to the photopic response curve of the human eye. The mean range of critical flash frequencies in 16 patients during eyes-open IPS was the same for white and green light but slightly less with red light. A significant finding was the reduction of the sensitivity range to blue light. Only one patient showed marked sensitivity to red light. The 2 patients who exhibited spike and wave during eyes-closed IPS, both showed increased sensitivity to red light and no sensitivity to blue or green. The authors propose the operation of the eyelid red-filter in these two cases. The VEP was not significantly altered by coloured light and, although occipital spikes occurred less frequently with coloured than with white light, there were no significant differences between the three colours.

2. EEG AND CLINICAL STUDIES

2.1. The Basic Record.

The EEG record of an epileptic patient may show abnormality between seizures as well as during an ictus Persistent abnormalities occur with traumatic epilepsy (Jeavons 1972a) but overall paroxystic activity is brief and episodic. About 60% of all epileptic patients are found to have a normal first EEG record (Jeavons 1974), although repeating the record increases the diagnostic success rate. Centrencephalic epilepsies are associated with bilateral discharges of spike and wave, slow waves, or spikes, whereas unilateral paroxysms indicate partial or focal epilepsy. Although it is uncommon for such abnormalities to occur in non-epileptics, they do not necessarily indicate epilepsy, nor does a normal EEG exclude the possibility of epilepsy (Jeavons 1972a, 1974). A limit exists, therefore, to the value of the EEG in diagnosing epilepsy but photosensitive epilepsy is always confirmed by abnormalities evoked by IPS (Ulett and Johnson 1958; Jeavons 1972b).

Only a few studies have commented on the condition of the basic resting record in patients with photosensitive epilepsy. Lloyd-Smith and Henderson (1951) reported that out of 40 epileptic patients with EEG activation during IPS, 13 (32.5%) had normal basic EEGs whilst in the remainder photic stimulation aggravated the abnormalities seen at rest or during hyperventilation. No characteristic basic EEG pattern for the photosensitive condition was found by Bickford et al. (1953). However, of the 27 children studied, the most common abnormality was diffuse high voltage 3 c.p.s., spike and wave occurring in 75% of the group. Focal

occipital sharp waves were seen in 18.5%. Herrlin (1954) was unable to draw any conclusions as to the nature of the basic EEG. In a series of children with a clear diagnosis of epilepsy, the incidence of photosensitivity was identical for those patients with normal or borderline routine EEGs and those with abnormal EEGs (20.4%). Capron (1966), examining the records of 161 photosensitive patients, found that 14% had normal EEGs before IPS.

2.1.1. Group differences.

Patients with a clinical history of fits only when viewing television appear to show less spontaneous 3 c.p.s. spike and wave abnormalities than patients who have fits at other times as well as with television (Jeavons 1966). Of 176 patients, 98 had seizures only when viewing television and at least half of these patients had normal routine EEGs , except during IPS (Jeavons and Harding 1970). Routine EEG abnormalities occurred in 54% of photosensitive epileptics, the most usual forms being bilateral 3 c.p.s. typical and atypical spike and wave discharge (Jeavons and Harding 1975). These authors classify their patients according to precipitation of fits (see Section 1.4). No significant difference was found between the different groups as regards the incidence of basic EEG abnormality. In a few cases spontaneous spike and wave only occurred after the patient had been exposed to IPS.

2.1.2. The effect of eye-closure.

Spontaneous abnormalities in the basic EEG are at times associated with the act of eye-closure. These discharges involve all cortical regions and it is important to distinguish them from the physiological response of eye-closure occurring in the posterior regions, particularly in

children during hyperventilation, and consisting of high amplitude slow waves (Jeavons and Harding 1975).

A frequent feature in the routine EEGs of children was rhythmical bursts of high voltage slow waves after eye-closure (Bickford et al. 1953). Of 1000 epileptic patients, epileptiform discharges were evoked in 29 cases (mainly women and children up to 10 years old) by eye-closure. The activity was especially vigorous after hyperventilation but none of the patients showed activation of the symptoms after IPS (Atzev 1962). Eye-opening, however, suppressed these EEG discharges and repeated eye-opening and eye-closure habituated the latter's effect on the EEG. Of 402 photosensitive epileptics, only 7% showed spontaneous spike and wave immediately following eye-closure (Jeavons 1966). Forster (1967) agreed that 'eye-closure dysrhythmia' was a rare manifestation and, in the dark, blinking and eye-closure may not evoke the abnormality (Forster 1967; Jeavons et al. 1972a).

Green (1966) reported the case histories of several patients who self-induced seizures by blinking in strong light. In one patient, spike and wave discharge was related to many but not all eye-blinks and seizures were associated with eye-closure. No seizures occurred with eye-closure in total darkness. Another patient showed EEG bursts with each eye-blink but mechanical movement of the lids in both patients completely failed to produce spike and wave. However, one child was able to induce seizure activity even in total darkness by eye-closure and, although mechanical holding of his eyelids prevented the EEG abnormality, it reappeared when he was able to roll his eyeballs underneath the eyelids. A report of 4 cases (Green 1968) showed that it was possible,

in individual patients who showed seizure activity on eye-closure, to elicit the abnormalities by mechanical movements of the lids and by eye-closure in total darkness, although this latter condition did result in a less intense seizure discharge.

A later study of 6 patients found disparity with Green's observations (Panayiotopoulos 1974). No patient showed an abnormal response on eye-closure in darkness and slow, passive eye-closure under normal illumination failed also to produce a response in 2 patients. Consistent abnormalities occurred when passive eye-closure was very fast. Spike and wave has been observed in 36% of 253 patients immediately following eye-closure and was associated, at times, with brief eyelid flutter or a slight, generalised myoclonic jerk (Jeavons and Harding 1975). The EEG discharges were not usually present in darkness. In one patient changing the direction of gaze and not blinking produced spike and wave. In another case, eye-opening was responsible for routine EEG abnormality in association with a myoclonic jerk. However, in other patients eye-opening may stop spike and wave bursts initiated by eye-closure (Green 1968).

As eye-closure induced abnormality has usually been reported as individual case studies, authors' theories of underlying mechanisms have been contradicted. Forster (1967) believed that a reduction or alteration of visual stimulation was due to the introduction of a red filter, i.e. eyelid capillary bed was operating during the act of eye-closure. However, the fact that eye-closure in total darkness may cause EEG activation shows that the physical factors of retinal illumination are not critical and so the idea of

eyelid red filters and diffusing the light, through closing the eyes and thereby illuminating a greater retinal area, are insufficient theories (Green 1966). Some cases imply the role of proprioreception by voluntary eye-closure (Green 1968). Atzev (1962) stated that the brain tonus is lowered by eye-closure and so will more readily induce triggering of an epileptogenic focus. It is possible that cerebral responsiveness is altered after closing the eyes as this action is frequently followed by 'squeak', i.e. activity which is about 2 c.p.s. faster than the basic alpha rhythm (Jeavons 1969).

Conflicting results in the literature may have arisen due to the study of different types of patients with different abnormalities; differences in the chosen criteria for abnormality associated with eye-closure, e.g. discharges occurring after 2 seconds of eye-closure are more related to the eyes-closed state; inclusion of fortuitous spontaneous abnormality during eye-closure in darkness (Panayiotopoulos 1974). This author also postulates that eye-closure is more provocative than eye-opening for evoking EEG abnormalities as more off-responses than on-responses are induced by light in the visual cortex.

2.2. EEG Responses to IPS: Their Clinical Significance

In the literature, the most frequently quoted abnormality evoked by IPS is generalised bilateral spike and wave, in particular the atypical 2.5-3.5 c.p.s. variety or polyspike and wave discharge (Lloyd-Smith and Henderson 1951; Bickford et al. 1953; Melsen 1959; Jeavons and Harding 1975). Only a few reports described abnormalities confined to the posterior cerebral regions (Lloyd-Smith and Henderson 1951; Naquet, Fergersten and Bert 1960; Jeavons 1969; Jeavons and Harding 1975).

Evaluation of the literature is difficult, not only because of wide variations in technique but also due to a lack of definition and illustration of EEG activity classified as abnormal. Watson and Marcus (1962) grouped five types of EEG activation together as 'photogenic cerebral electrical abnormalities' but only one variable, i.e. multiple spikes or spike and slow wave could be considered as true abnormality. The combination of specific and non-specific EEG responses to IPS produces a high incidence of photosensitivity. Herrlin (1954) quotes a 10 - 30% occurrence of pathological activity during IPS in children. Finding that 24.5% of a psychiatric sample showed a marked or extreme (paroxysmal) activation, Ulett and Johnson (1958) believed it to be indicative of a low convulsive threshold and stressed the clinical importance of photic activation.

Troupin (1966) stated that EEG photosensitivity was probably more than a chance occurrence but that it was not diagnostic of a specific disorder. A survey of 14,141 cases showed an incidence of spike and wave discharges of around 2% (Jeavons 1966). A diagnosis of photosensitive

epilepsy is, however, always clarified by the presence of IPS induced spike and wave, although a few authors reported occasional cases with diagnosed 'television- epilepsy' but no abnormality during IPS (Klapateck 1959; Charlton and Hoefer 1964).

Variation exists in authors' classification of photic responses according to morphology, location and clinical significance. Bickford et al. (1952) distinguished between the photomyoclonic response (PMR) and the photoconvulsive response (PCR). The former appeared when the eyes were closed, occurred frequently in normals, was more common in adults, had a clinical accompaniment of muscle jerking and consisted of anterior polyspikes in the EEG. On the other hand, the PCR occurred with eyes-open or closed, was rarely found in normals, had a clinical accompaniment of turning the head or speech arrest and was seen in all EEG regions as spike and wave. Besides these two responses, Melsen (1959) also defined two other types of paroxysmal activity, i.e. high amplitude bilateral slow waves contrasting with the background rhythm, often with an irregular spike component; and focal spikes or sharp waves. Capron (1966) classified 7 types of photically evoked abnormality including classical and atypical spike and wave forms, clinical fits, degraded spike and wave, theta and delta forms of occipital spike and wave, recruitment of occipital rhythms at 7 - 9 c.p.s. spreading to fronto-rolandic regions with myoclonic jerks, and the PMR. Undoubtedly the clearest definition of IPS induced abnormalities is in relation to EEG distribution as follows (Jeavons 1969: Jeavons and Harding 1975):-

(i) The response is seen only in the anterior regions: photomyoclonic response;

(ii) The response is eeen only in the posterior regions: photic driving, visual evoked potential (VEP), occipital spikes;

(iii) The response is widespread, bilateral and involves anterior and posterior regions: photoconvulsive responses.

2.2.1. The photomyoclonic response.

The photomyoclonic response (PMR) is registered in the prefrontal and frontal leads of the EEG as muscle spike (polyspike) potentials around the eyes and results in eyelid flutter (Lloyd-Smith and Henderson 1951; Melsen 1959; Jeavons 1969; Hess et al. 1974). Occasionally the response may spread to other facial muscles and, under a pathologically intense stimulus, to other body muscles at a rate of 30-40 m/sec. producing generalised myoclonic jerking (Lloyd-Smith and Henderson 1951; Bickford et al. 1952; Jeavons 1969). Meier-Ewart and Broughton (1967) regarded this as a summatiom of subclinical physiological reflexes. The muscle spikes are rhythmic and show recruitment, with the most effective light stimulus frequencies between 6-20 f.p.s. (Lloyd-Smith and Henderson 1951; Bickford et al. 1952; Meier-Ewert and Broughton 1967; Hess et al. 1974). The PMR is a diphasic potential with a duration of 15-20 msec. occasionally followed by multiphasic potentials. Stimulus-locked components have been observed at 40-50 msec., 70-80 msec. and 105-115 msec. but there is controversy as to whether the first or second potential is the basis of the PMR (Meier-Ewert and Broughton 1967). Green (1969) recorded a large

negative wave at 55-60 msec. with eyelid electrodes in both photosensitive patients and controls with eyes-closed and believed the potential represented a PMR.

The PMR is mainly a response to high intensity light when the eyes are closed. The response ceases when IPS is stopped and is usually inhibited by eye-opening (Bickford et al. 1952; Melsen 1959; Jeavons 1969). Covering one eye when both are already closed will also inhibit the response (Bickford et al. 1952). These authors observed that increased muscle tension and nervousness increased the PMR and that repeated testing in the same subject caused a gradual disappearance of the response due to increased relaxation and changes in facial tonus of the subject.

The maximum amplitude of the PMR is around 1 mv. but, unlike latencies, the amplitude is variable (Melsen 1959). The response has no after-discharge and is of negligible amplitude in the occipital regions (Bickford et al. 1952; Green 1969). In rare instances the PMR may precede a generalised seizure (Lloyd-smith and Henderson 1951) but normally IPS may continue for a long time without loss of consciousness or subjective changes in awareness (Bickford et al. 1952; Melsen 1959; Hess et al. 1974). The response, therefore, appears to have little clinical significance (Jeavons 1969). Melsen (1959) found that the PMR was as probable in 'cryptogenic', symptomatic and suspected epileptic groups and regarded the response as non-specific. Myoclonic jerking of the facial muscles was observed in 10 out of 20 healthy, normal subjects (Bickford et al. 1952) and has little correlation with epilepsy, although it can be seen in parents of children

with a photoconvulsive response (Troupin 1966). The PMR was also observed in a clinically mixed group of patients with a wide variety of illnesses (Bickford et al. 1952). They found that the threshold of response decreases with age, being rarely seen in children and more common in adults.

Of 72 photosensitive patients, 29% exhibited only a PMR, while 14% showed a PMR together with spike and wave discharge (presumably with eyes closed). Administration of metrazol increased the incidence of a PMR to 78% of patients during IPS (Bickford et al. 1952). Intravenous valium, however, suppressed the PMR and peripheral body jerks by decreasing muscle tone. The PMR reappeared after 80-160 minutes (Ebe, Meier-Ewert and Broughton 1969). From these studies it was surmised that the stretch reflexes facilitate the appearance of a PMR. The short latency, frequent absence of a recordable correlate in the cortex, and the fact that a PMR can continue in decorticate animals (Meier-Ewert and Broughton 1967) suggest that short subcortical pathways mediate the PMR and not purely corticospinal mechanisms. In some cases a PMR may develop into a photoconvulsive response (Bickford et al. 1952). In such patients an interaction may exist between the two systems of a progressively increasing, positive feedback of proprioreceptive impulses.

2.2.2. The photoconvulsive response.

The photoconvulsive response (PCR) usually encompasses generalised, bilateral spike and wave activity of 2-5 c.p.s. more than 100-200 μv in amplitude with polyspikes, irregular spikes, or without spikes, and was originally known as 'spike and dome' complexes (Herrlin 1954; Marshall et al. 1953; Pantelakis et al. 1962;

Wadlington and Riley 1965; Hishikawa et al. 1967; Meier-Ewert and Broughton 1967). This description includes classical 3 c.p.s. spike and wave together with other mutated forms of response. The PCR shows great variation and it is possible to find several types of response in the same patient, also the responses may vary from time to time (Jeavons 1969). The characteristic feature of the PCR is that it is bilaterally widespread and involves anterior and posterior regions. A preponderance of pathological activity in only one hemisphere is infrequent (Herrlin 1954). Jeavons and Harding (1975) described 6 types of PCR.

(i) Bursts of spike and wave activity which are often irregular, with a slow component usually at 3 c.p.s;

(ii) Bursts of high amplitude theta waves (4-7 c.p.s.) with spikes (theta spike and wave);

(iii) Bursts of polyspikes or polyspike and wave;

(iv) Bursts of widespread spikes at the same rate as the flash;

(v) Discharges of 3 c.p.s. spike and wave persisting more than 5 seconds after the flash has ceased, and associated with clinical absence;

(vi) Bilateral generalised slow waves without spikes.

Degraded PCRs may occur at the start of the train of flashes or after stopping IPS. These are called on- and off-responses and may occur alone or together. It is possible for the PCR to change within the duration of a flash train. Hutt et al. (1963) observed in 4 photosensitive epileptic children that the PCR initially consisted of multiple spikes at the frequency of the flash, followed

1-2 seconds later by the gradual appearance of a slow wave component which replaced the spike discharge and persisted for several seconds. Each response began within 0.1 to 0.5 seconds after the start of flicker. Jeavons and Harding (1975) stated that the nature, onset, duration and range of flash rates which evoked the PCR were not of diagnostic importance but only the consistent propagation of a PCR at a number of flash rates was diagnostically significant.

Several authors have commented on the lack of similarity in some cases between spontaneous EEG paroxysms and those evoked by IPS in the same patient. Hutt et al. (1963) suggested that the spread of the discharge differed under both conditions. Resting EEG patterns were not found to be indicative of whether the subsequent PCR was precipitated by occipital abnormality or appeared simultaneously over all areas (Hishikawa et al. 1967). However, PCRs at 3 c.p.s. have been found to be more common in patients with abnormal basic records, while theta spike and wave were more frequent in those with normal routine EEG records. Fewer of these latter patients had photosensitive epilepsy (Jeavons and Harding 1975). Spike and wave PCRs at 3 c.p.s. were observed in 88% of patients, 7% had theta spike and wave and 3% had other forms of PCR.

Photic stimulation may also induce subjective sensations of faintness, dizziness, unpleasantness or jerking even in the absence of actual jerks (Marshall et al. 1953; Melsen 1959; Jeavons and Harding 1975). Pleasant feelings of awareness have also been reported (van Steenbrugghe and Lairy 1965). Peculiar sensations are usually associated

with an abnormal discharge of spike and wave (Jeavons and Harding 1975), and some patients experience the same feeling during IPS as with flickering light in the everyday situation.

During intense stimulation or in hypersensitive patients it is possible to evoke a seizure. These generally take the form of absences, eyelid fluttering or myoclonic jerks, but generalised convulsions may occur under prolonged IPS (Bickford et al. 1952; Melsen 1959; Jeavons 1969; Hess et al. 1974). PCRs are variable and generally occur with equal frequency among the different clinical groups, i.e. the clinical history is not suggestive for a particular form of PCR (Herrlin 1954; Jeavons 1966; Hishikawa et al. 1967). However, when a seizure is evoked by IPS, the EEG response is more typical of that seizure type (Bickford et al. 1952; Herrlin 1954). Absence seizures are associated with tyical and atypical 3 c.p.s. spike and wave discharges which may be persistent. Similar abnormality may be seen in the basic record. Myoclonic jerks are accompanied by polyspike discharges during IPS and occur in about 21% of photosensitive epileptics, of which two-thirds have abnormal basic records. Herrlin (1954) reported that in a few cases IPS triggered a clinical seizure of a different nature to that occurring spontaneously.

The PCR has been associated with idiopathic, in particular centrencephalic, forms of epilepsy rather than the acquired symptomatic varieties (Pantelakis et al. 1962; Troupin 1966). It may also occur, however, in febrile convulsions, psychomotor seizures, other forms of epilepsy

and neurovegetative disorders (Doose et al. 1969b; Gerken and Doose 1969). Conclusions as to the clinical significance of the PCR have been drawn from EEG data analysed over ten years (Jeavons and Harding 1975). They found that although PCRs do not necessarily indicate a clinical diagnosis of photosensitive epilepsy, there is an 80% chance that the patient does not have an epileptic condition providing there is no relative with photosensitive epilepsy. A normal basic EEG at rest and during hyperventilation is no criterion between a non-photosensitive person and an affected individual. However, spike and wave following eye-closure usually guarantees that a PCR will be found on IPS. Most of these patients, and all patients with a polyspike PCR, suffer with epilepsy. Similarly a diagnosis of this condition is virtually certain when myoclonic jerks accompany the PCR.

2.2.3. Occipital abnormalities.

Various authors have focused attention on the clinical signifance of occipito-parietal theta waves at 3-7 c.p.s. in the resting EEG. These waves tend to be bilateral and solitary and have been linked with maturational processes (Aird and Gastant 1959). Marked changes in EEG frequency of the parietal-occipital rhythms have been noted with increasing age (Corbin, Pennel and Bickford 1955). They found that the abnormality rate was higher in children than in adults, indicating that sharp wave discharges in that area had little pathological significance and reflected an increasing stability with maturation. However, abnormal theta rhythms, part-

icularly of the posterior regions, have been linked with a genetic susceptibility to convulsions (Taistra, Gerken and Doose 1976). The rhythm was reported as being age dependant, with the highest incidence during 2-5 years, and associated with the centrencephalic epilepsies of early childhood. The symptom was more pronounced with boys than girls, and up to 15% of healthy children also showed abnormal theta rhythm the background EEG.

During IPS similar phenomena have been observed. Walter et al. (1946) observed that in subjects with theta in the basic EEG, subharmonic responses were prominent at frequencies of 8-14 f.p.s.. Bilateral occipito-parietal high amplitude slow waves were found in 11.6% of 120 nornal children during IPS. Children above 15 years of age showed no such response (Brandt et al. 1961) and the authors, believing this EEG pattern reflected cerebral maturity, warned against hazardous diagnosis. Similar phenomena were seen in epileptic and non-epileptic children and were regarded as clinically insignificant (Gerken et al. 1968).

Capron (1966) noted that IPS could elicit theta spike and wave and also recruitment of occipital waves at 7-9 c.p.s. spreading to the fronto-rolandic region with myoclonic jerking. Occipital spikes or occipital pseudo-spike and wave, fundamental to the flash rate is thought to represent an exaggerated visual evoked potential (VEP) and hence a photosensitive response (Jeavons 1969). However, this type of response may be present in non-epileptics and those not suffering with photosensitive epilepsy. Occipital spikes are time-locked to the flash and show

phase reversal and maximal amplitude at the occipital electrodes. The major component is electronegative with small preceding and following positive deflections (Panayoptopoulos, Jeavons and Harding, 1970; 1972). The amplitude of the most constant (negative) component is generally between 60-100 μv but may exceed 150 μv on occasions (Jeavons and Harding 1975). Combination of fast paper speeds, increased gains and special montages illustrate the occipital spikes more clearly, particularly when few in number and of small amplitude, as when immediately preceding a generalised discharge.

Hishikawa et al. (1967) were the first to classify the PCR based on localisation of the early components. Of 15 photosensitive patients, 8 had distinct occipital discharges which preceded the generalised simultaneous spread to other areas. Other authors have reported a rare incidence of occipital spike foci which are fired by IPS up to 6 f.p.s. and indicate a triggering effect (Lloyd-Smith and Henderson 1951; Rodin, Daly and Bickford 1955). Gastaut et al. (1961) observed in 3 epileptic children that IPS evoked tonic-clonic seizures which were first noticed in the occipital EEG regions.

The incidence of occipital spikes appears to be related to the technique of IPS adopted. White light is more effective in evoking the abnormality than coloured lights (Harding, Pearce, Dimitrakoudi and Jeavons 1975), and patterned flash is very provocative (see Section 2.5). Using a fine grid mesh, 87% of photosensitive epileptics had PCRs precipitated by occipital spikes (Panayiotopoulos et al. 1972). In two-thirds of the patients,

these spikes appeared at low flash rates and it was surmised that prolonged IPS at these frequencies would have evoked PCRs. One-third had PCRs triggered by occipital spikes at flash rates greater than 11 f.p.s.. These authors determined that the spikes first appeared between 200 msec. to 3 seconds after onset of the flash but never in response to the first flash. In the majority of cases, increase in flash rate up to 9 f.p.s. caused a successive increase in amplitude of the spikes. Continuation of the flicker at around 5 - 7 f.p.s. resulted in either a waxing or waning of amplitude or the response terminated in a PCR. Maheshwari and Jeavons (1975) were able to distinguish occipital spikes from harmonic photic driving responses, as the former were of constant duration and latency, regardless of flash rate; they occur later than photic driving but appear earlier with increase in flash frequency.

Although occipital spikes precede a PCR, they may occur alone. However, this is a rare response occurring in about 0.6% of photosensitive patients (Maheshwari and Jeavons 1975). These authors studied occipital spikes in 45 patients (epileptic, non-epileptic and photosensitive) over a 9-year period. The spikes were not consistently present between EEG recordings and, when no concomitant PCR existed, they were suggestive of a non-specific abnormality and not indicative of epilepsy. The presence or absence of spike abnormality in the basic EEG did not appear to be related to the presence of photically evoked occipital spikes. Phenobarbitone and other antiepileptic drugs did not appear to influence the response. In fact the only common factor in all types of patient with occipital spikes

was the preponderance of females (male:female ratio approximately 1:2).

There have been several reports of the epileptogenic nature of the occipital lobes in man and animals. Spontaneous or photically activated ictal or interictal EEG discharge may occur locally or propagate rapidly to all regions from an obvious epileptogenic focus or an area of supposed cortical hyperexcitability (Naquet et al. 1960; Ludwig and Marsan 1975). This type of focal seizure has been paralleled to temporal lobe epilepsy and termed occipital lobe epilepsy (Huott, Madison and Niedermeyer 1974). It differs from idiopathic, photosensitive epilepsy in that focal repetitive spikes are the most common EEG paroxysm, and bilateral synchronous spike and wave complexes are infrequent, suggesting a different underlying mechanism. Irradiation of EEG abnormality is usually restricted to the hemisphere in which the paroxysm originated, sometimes with no modificatiom of the background activity in the contralateral hemisphere. At other times, background rhythms are slowed on both sides (Naquet et al. 1960). Variations in subjective sensation may also be evidential of different mechanisms. The classical photosensitive epileptic may experience unpleasant feelings of changes in awareness; the patient with clearly focalised cortical occipital lobe epilepsy may experience visual hallucinations and cortical blindness. The only similarity in clinical effect during IPS is the involvement of the motor cortex, resulting in myoclonic jerks in the former and mystagmus in the latter patients (Huott et al. 1974).

2.2.4. Photic driving.

Photic driving or photic following is a rhythmical response to a regular train of flashing light greater than 5 f.p.s.. It is seen predominantly over the occipito-parietal areas as fundamental, harmonic or sub-harmonics of the flash rate (Adrian and Matthews 1934; Werre and Smith 1964; Troupin 1966; Jeavons 1969). The waveform is often sharp and sinusoidal, one half cycle being pointed which may indicate the presence of higher order harmonics (Walter et al. 1946; Jeavons 1969). Although photic driving can be detected by visual inspection of the EEG, low frequency analysis and averaging techniques are required to determine the presence of these higher order harmonics which may be unobservable in the raw EEG (Walter et al. 1946; Werre and Smith 1964; Jeavons 1969).

The term 'photic driving' was originated by Adrian and Matthews (1934) who believed that the response was due to driving of the 'Berger' (alpha) rhythm by IPS at flash rates from 10 - 20 f.p.s.. This driving was particularly regular and persistent when the flash rate coincided with the resting alpha frequency. Since then, there has been much controversy as to the relation of photic driving with background EEG activity. The nature and extent of the response has been linked with the predominant EEG activity, alpha rhythm and prominence of beta rhythm (Walter et al. 1946; Marshall et al. 1953; Barlow 1960; Hughes 1960). However, other authors have denied any association with dominant alpha or spontaneous EEG frequencies (Cigánek 1961; Keesey 1971; Kinney, McKay, Mensch and Luria 1973). Ulett and Johnson (1958) suggested that the activity evoked by IPS was

not simply an augmentation of spontaneous brain activity, but that other neural units became involved. It is apparent that much of this disparity might have arisen from some authors recording with eyes-open and others with eyes-closed, as the latter increases the correlation between the frequency of the resting activity and photic driving.

There exists a great deal of intra- and inter-individual variability as regards the effect of stimulus parameters and mental activity on the amplitude, frequency, uniformity and consistency of photic driving (Adrian and Matthews 1934; Walter et al. 1946; Butcher and Chase 1965). The poorest response was found in the first EEG recording and attributed to subject tension (Ulett and Johnson 1958). Donker (1973) observed that amplitude variations occurred in all scalp areas and early work showed that good photic driving depended on stimulating a wide visual field (Adrian and Matthews 1934). When limited to the central vision, photic driving became small and irregular. A shift in gaze of 12 - 15^{o} to the edge of the lamp has been found to inhibit the response (Jeavons et al. 1972a).

Higher flash rates with patterned stimulation were seen to cause an amplitude reduction in photic driving (Adrian and Matthews 1934). Comparison of evoked potentials to blank and striped fields however, was later found to have no differential effect of flash rate. Both types of stimuli decreased the mean amplitude of response at frequencies above 8 f.p.s. and both increased variability at fast flash rates. Analysis of variance showed no significant pattern effect nor a significant interaction

between pattern and flash as regards amplitude (Kinney et al. 1973). Pattern stimulation may, however, produce different types of photic driving.

Increase in flash frequency shortens the inter-stimulus interval, and above 5 f.p.s. a 'telescoping' of response occurs producing sinusoidal activity on which may be superimposed small deflections (Van Hof 1960; Werre and Smith 1964). Reducing the interstimulus interval is thought to create an overlap of components. Werre and Smith (1964), when recording VEPs with double flashes using short inter-stimulus intervals, found that the second flash accentuated the first potential producing a sinusoidal waveform. Observing a marked reduction in amplitude at high flash rates, Kinney et al. (1973) ascribed it to formation of the response from composite portions of the complete evoked potential, as a result of either a real stimulus effect, or simply the result of adding a large preceding negative component to a large positive component at the onset of the next potential. This apparent overlap of components led several authors to predict the photic driving response at higher flash rates by linear superimposition of evoked potential components at low flash rates. Agreement was found between synthetic and actual evoked responses for flash rates between 5 - 11 f.p.s. (Van Hoff 1960) and mainly in subjects who showed consistent deflections at very low frequencies (Rietveld 1963). The relationship, however, broke down at high flash rates and Van Hoff (1960) believed this to be due to the culmination of frequency, duration and intensity producing too much 'total integrated light flux'.

Rietveld (1963) disputed this theory as he was able to predict similarly between synthetic and actual responses for low and high intensity light. Werre and Smith (1964), although supporting these findings to some extent, introduced variability by including the after-discharge in their analysis. Inclusion of the after-discharge was shown to ruin the synthetic sinusoidal pattern of photic driving (Kinney et al. 1973). In fact the rhythmic after-discharge remains unaltered when increasing flash rate until it disappears, due to the short inter-stimulus intervals (Cigánek 1961).

Cigánek (1961) drew a distinction between photic driving up to 10 c.p.s., which retained the 'primary response' up to about 90 msec., and that resulting from frequencies at 16 - 30 f.p.s., which produced the 'deformed sinusoidal curve'. He postulated that both types of response originated from different brain regions, the latter arising from non-specific thalamic nuclei. Adrian and Matthews (1934)had cited the occipital lobe as the generator of photic driving, due to its similarity with the alpha rhythm. Finding a photic driving response in amblyopic children, Parsons-Smith (1953) stated that perception of light was the essential requirement and not pattern vision. As flicker rates approach the alpha frequency, there is a progressive reduction of inhibitory post-synaptic potentials (IPSPs) and an unmasking of excitatory post-synaptic potentials (EPSPs), (Kuhnt and Creutzfeldt (1971). Peacock (1973) postulated that a difference in equilibrium of both types of PSP between the occiput and vertex at around 10 c.p.s. could cause a

sudden loss of the vertex response by reduced inhibition which, in turn, would initiate excitation. Such repeated firing would result in desynchronisation of cortical electrical activity, seen as random noise in the EEG. The author noted that at high frequencies the vertex appeared to be unresponsive, whereas the occipital lobes continued to produce sinusoidal response and therefore proposed the involvement of mechanisms other than those involved with primary sensory input.

Shagass (1955) reported that the quality of photic driving was related to age. From about 4 months old, cerebral responsiveness to IPS improved until at 10-14 years a marked increase in power spectra was observed in the secondary harmonics of flash rates up to 20 f.p.s. with an optimum at 10 f.p.s. Several authors have found the amplitude of photic driving to be increased in females (Shagass 1955) and to vary with their menstrual cycle (Vogel, Broverman and Klaiber 1971). Vogel and his colleagues have discovered by treating amenorrheic women with hormone therapy and by monitoring plasma monoamine oxidase (MAO) activity in males and females, that low oestrogen encourages high MAO activity, which in turn reduces central adrenergic neurotransmission. Such conditions produce high photic driving, whereas a low driving response occurs under high levels of oestrogen, as seen in the preovulatory stage of the menstrual cycle. Testosterone, the male gonadal steroid hormone, had a similar action to oestrogen. Administration of a MAO inhibitor had no effect on the background alpha activity. It seemed obvious, therefore, that photic driving is

related to nor-adrenergic transmission in the brain (Vogel et al. 1971; Vogel, Broverman, Klaiber and Kobayashi 1974).

During photic driving, individuals may not be aware of any subjective change (Adrian and Matthews 1934), while others can experience sensations, particularly when the response extends from the visual projection areas (Walter et al. 1946). Quantitative differences in photic driving have been linked with changes in emotional states in psychiatric patients, especially when female (Shagass 1955). However, in normal subjects no such relationship appears to exist (Ulett and Johnson 1958). Golla and Winter (1959) differentiated between three patterns of photic driving response in connection with the presence or absence of headaches. Migrainous patients showed extended driving over 8 - 26 f.p.s..

Variability of photic driving is particularly evident at high flash rates (Kinney et al. 1973). Due to such intra and inter-variability, some authors have tried to assess the clinical significance of photic driving using asymmetrics or more than 50%, or lack of correlation between harmonic or fundamental response between the two hemispheres, as diagnostic criteria. Of 54 epileptic patients with focalised or propagated abnormalities of the occipital lobe, 13 showed better photic driving over the occipital area least involved in the epileptic process. This suggests mutual exclusiveness of photic driving and paroxysmal activity. However, the frequencies evoking the former response are also the critical frequencies for epileptic activation (Ciganek 1961). Examination of first

routine EEG records showed considerable variability in photic driving, but 12-18 f.p.s. was effective in most patients (Hughes 1960). Children with definite or questionable epilepsy more often reacted with subharmonic responses of increased amplitude (Herrlin 1954), but this may have been associated with basic EEG activity, as Walter et al. (1946) found subharmonic responses at 8 - 14 f.p.s. in subjects with prominent 4 - 7 c.p.s. theta in the basic record. Investigating the possibility that within subject amplitude variation might equally influence homologous hemispheric regions, these authors discovered that statistical significance could exist between these areas particularly for the fundamental rather than the secondary harmonic response.

Photic driving is a normal response (Jeavons 1969) and its clinically significant role is tentative. Walter et al. (1946) observed that secondary and tertiary harmonics could have different topographical distribution from that of the fundamental frequency and that they reacted differentially to changing states within the subject. Brazier (1953) commented on the clinical importance of these harmonics and queried whether they represented activity from different neuronal aggregates, each discharging a real and syncopated response, or whether they were a true multiple response from one group of cells. She postulated that if the cortex were not a way station for pathological photic activation in the photosensitive epileptic, the patient might be insensitive to rhythmic secondary harmonics in the cortex at the same frequency as that of a critical flash rate, e.g. a PCR might be con-

sistently evoked at 12 f.p.s. but an harmonic response at 12 c.p.s., produced by a flash rate of 6 f.p.s., would not activate spike and wave discharge. Her hypothesis supports the idea of mutual exclusiveness of the paroxysmal and the occipital driving response.

2.3. The Sensitivity Range.

The photosensitivity range has an upper and lower limit which are defined as the highest and lowest flash rate which consistently evokes a PCR (Jeavons and Harding 1975). Subtraction of the two limits gives the actual range of critical frequencies. A review of optimum flash frequencies is given in section 1.8.. Although many authors agree that the most provocative flash rates are between 10 - 20 f.p.s., testing has usually stopped around 30 f.p.s.. It is possible for a few patients to show a PCR at 1 f.p.s. or at rates above 60 f.p.s. (Jeavons and Harding 1975). Diagnostic studies have been conducted using only a few critical frequencies or even one frequency. Melsen (1959) made comparisons using only the lower limit and called it the 'activating frequency'.

Few authors have systematically determined the sensitivity range for individual patients (Pantelakis et al. 1962; Wadlington and Riley 1965; Jeavons 1969; Jeavons and Harding 1975). The usual procedure was to initially screen patients for photosensitivity at rates of 16 or 20 f.p.s. for 10 seconds with eyes-open and/or eyes-closed. Testing then normally began at the lower frequencies with successive increase in flash rate until abnormality was evoked. Jeavons and Harding (1975) used odd numbers to reduce interference from harmonic photic driving. Interstimulus intervals of 10 seconds were left between each flicker sequence to allow for recovery of the EEG and to avoid habituation or sensitisation to the flash. Instead of proceeding through all frequencies, when the lower limit of the sensitivity range had been established, these authors switched to high frequency stimulation and reduced the flash rate in steps of ten until abnormality occurred. The exact upper limit was then

determined by gradually varying the flash rate in steps of 2 f.p.s..

These authors differentiated between narrow ranges, up to 34 flash frequencies, and wide ranges, greater than 34 flash frequencies, for 157 patients. The only clinically significant finding was that wide ranges were more common in patients only flicker sensitive (Group 1) than in those patients who either, or also, had spontaneous fits (Groups 111 and 11). Although Group 1 included those patients with 'television-epilepsy', the width of the sensitivity range was not related to close viewing of the television set. They concluded that the sensitivity range is of no apparent clinical significance but that the sensitivity limits and actual frequencies evoking a PCR are important from diagnostic and therapeutic considerations.

2.4. Eye States.

2.4.1. Monocular stimulation.

Many authors have reported on the reduction or abolition of abnormalities induced by IPS by covering one eye, and several investigations have attempted to employ monocular occlusion into therapeutic techniques for photosensitivity. A review of this literature is discussed in sections 3.1. and 3.2..

A typical example is found in Hishikawa et al. (1967). Of 15 patients 14 showed no PCRs when one eye was occluded, even when IPS was prolonged. Although paroxysms were still present in one patient they were diminished and of longer latency. Similarly, during binocular stimulation of 3 patients, a 50% reduction in the intensity of prolonged IPS failed to evoke PCRs. The authors linked these monocular effects with the reduction in the extent of retinal surface illumination. Highly degraded spike and wave was observed during monocular stimulation, and then only at higher intensities, in comparison to the PCRs evoked with patterned flash to both eyes (Chatrian et al. 1970a). These diminished responses were attributed to a critical reduction of input to visual cortical neurons. In 3 cases of amblyopic strabismus, suppression of the amblyopic eye may have been operating when epileptiform activity occurred with binocular stimulation and monocular stimulation to the sound eye but negligible activation was seen with the amblyopic eye (Parsons-Smith 1953).

The fact that the area of visual field stimulated or intensity of the light has to be doubled during monocular stimulation to produce a response comparable with that obtained on binocular stimulation, indicates that the former condition

causes a reduction of about 50% in the firing of visual cortical cells, so that the resulting electrical activity is well below the PCR threshold. Hubel and Wiesel (1959; 1962; 1968) have mapped the receptive fields in the visual pathways of the cat and monkey. The monkey comes close to man in its visual capabilities with high acuity and colour vision. The first point at which nerve cell convergence from both eyes occurs in the primate visual pathway is at the lateral geniculate body. This six layered structure contains the nerve fibres from each eye in alternate layers with minimal overlap. Therefore, negligible activity occurs in half of the lateral geniculate during monocular stimulation. In the visual striate cortex these authors discovered a predominance of complex and hypercomplex cells driven by binocular stimulation. When corresponding retinal parts of both eyes were stimulated summation occurred. However, the relative influence of the two eyes differed, in some nerve cells each eye contributed equally, in others one eye dominated. Jeavons and Harding (1970) observed that in photosensitive patients some showed less abnormality with one eye then the other. Studies of primate cortex show that some visual units do not respond to either eye alone but can only be activated by simultaneous stimulation of both eyes. Also, only relatively few units exist which are in fact simple cells and are only monocularly driven (Hubel and Wiesel 1959; 1962; 1968). It is evident anatomically, therefore, that monocular stimulation greatly reduces the potential excitation of sub-cortical and cortical visual pathways.

2.4.2. Position of the eyelids.

Over the last 25 years many authors have supported the notion that abnormalities were mainly induced by IPS when

the eyes were closed and were suppressed or abolished with open eyes (Brazier 1953; Pallis and Louis 1961; Atzev 1962; Pantelakis et al. 1962; Wadlington and Riley 1965; Bickford and Klass 1969). Only a few reports found greater abnormality during IPS with eyes-open (Mawsdley 1961; Jeavons et al. 1966). Several theories arose to account for the apparent eyes-closed effect. It was postulated that the eyelids acted as a red filter (Carterette and Symmes 1952; Bickford et al. 1953; Troupin 1966) and increased sensitivity was primarily due to the integration of red carrying elements at the lateral geniculate body (Marshall et al. 1953). However, the differential effects of coloured light is controversial (see section 1.13.). Less activation was found with eyes-open using a red filter than on testing with eyes-closed (Troupin 1966) and others dispute the efficacy of coloured light over white light in evoking the PCR (Harding et al. 1975). The red-filter theory was considered insufficient and it was proposed that during eyes-closed enhancement of the PCR occurred due to diffusion of light which stimulated a greater retinal area (Brausch and Ferguson 1965; Green 1966). Loss of visual attention (Pantelakis et al. 1962) and reduction of visual pattern input (Bickford and Klass 1969) were also linked with this phenomenon.

Much of the discrepancy in the literature has arisen from failure to distinguish between eyes-open, eyes-closed, and eye-closure (Jeavons and Harding 1975). It appears to be common practice to instruct the patient to close his eyes during IPS, a technique definitely used by Pantelakis et al. (1962) and Capron (1966). In many cases increased sensitivity with closed eyes was in all probability due to the act of eye-closure.

Eye-closure may readily evoke abnormalities in the spontaneous EEG (Bickford et al. 1953; Atzev 1962; Jeavons 1966; Green 1968) and blinking or eye-closure is also capable of inducing fits (Andermann et al. 1962; Green 1966; Forster 1967; Bickford and Klass 1969). In particular, eye-closure is very effective in evoking abnormal responses during IPS (Herrlin 1954; Capron 1966; Jeavons 1966). Sensitivity ranges were established in 292 patients (Jeavons and Harding 1975). Most were more sensitive with eyes-open than eyes-closed (88%) and 60% were sensitive only with eyes-open. Wide sensitivity ranges were more common for eyes-open sensitivity than for eyes-closed. In 3% of cases, where neither condition evoked abnormality, a PCR occurred following eye-closure. The authors concluded that in order of effectiveness, eye-closure was greater than eyes-open which in turn was greater than eyes-closed.

It is thought that the act of eye-closure lowers the brain tonus and may readily trigger epileptogenic areas (Atzev 1962). A faster alpha rhythm ('squeak') is seen in patients and normals immediately after eye-closure. It is interesting that eye-opening can inhibit a PCR present during eyes-closed (Brazier 1953; Jeavons - personal communication) besides blocking the PMR (Bickford et al. 1952).

2.4.3. Direction of gaze and lateral illumination.

In 1953 Marshall et al. reported that in one photosensitive patient unilateral IPS had inhibited seizure progression. Subsequently, there was little mention of this effect in the literature until Jeavons (1969) stressed that direction of gaze was probably more important in evoking a PCR than distance from the lamp or equal illumination of both eyes. Fixation onto the centre of the lamp would stimulate

the maximum number of retinal cells.

It was found that shifting the direction of gaze by 12 - 15° to the edge of the lamp suppressed or abolished the PCR in 9 out of 18 patients (Jeavons et al. 1972a). Further investigation by these authors showed that gazing to the far right or left abolished the PCR in 98% of patients even at very high intensities. Similar results were obtained with upward or downward movement of gaze. They observed that unilateral illumination at 90°, 45° and 30° from the visual central meridian was ineffective in evoking PCRs. As unilateral illumination at 90° was equivalent to monocular stimulation through nasal shielding, two stroboscopes were placed at the same angle either side of the head and triggered simultaneously at the same rate. No PCRs were evoked unless the patient was directed to gaze at one of the lamps.

These authors recommended that during IPS the lamp should be placed at about 30 cms. to allow the patient to focus on the centre of the screen and to enable monitoring of any unwanted eye-movements. Jeavons and Harding (1975) also proposed that purely flicker-sensitive patients with normal EEGs would be safe to drive as flickering light through railings or an avenue of trees would be at the side of the driver and not within his central field of vision.

2.5. Pattern.

In the case report of one very photosensitive woman, Goodkind (1936) mentioned that her myoclonic jerking was particularly severe when sunlight streamed into a darkened room through a wire-meshed window. Other anecdotal reports followed of photosensitive patients (some of whom self-induced attacks) who had types of absence fits when gazing at striped clothing, checked fabric, radiators, grids, perforated zinc sheeting or black lines on a white background (Bickford et al. 1953; Andermann et al. 1962; Forster 1967). It was found that pattern was an effective stimulus for producing a PCR even when the pattern was not flashed-on or moved (Troupin 1966). Evidence of pattern-sensitivity was found in 5% of photosensitive patients (Bickford and Klass 1969), the optimum stimulus being simple, fine geometrical designs.

Chatrian et al.(1970a) reported four cases of pattern-sensitive epilepsy. Two of the patients were brothers, thereby suggesting a genetic influence. The most effective triggers for abnormal EEG discharge were sharply contoured, highly contrasted parallel lines, particularly when centred onto the macula's visual field. Another eight cases were described by Jones et al. (1976). Clinical seizures of absence attacks or generalised tonic-clonic convulsions were evoked by striped clothing, floor grills, fences, riding escalators and 'Op-Art'. Four patients had also experienced fits in front of the television. The influence of moving pattern in 'television epilepsy' from simulated line-jitter and picture formation was tested by Darby et al. (1977). Of 28 photosensitive patients, 17 were pattern-sensitive as well

as clinically sensitive to the television. Four other cases were pattern-sensitive but had no clinical association with television. The link between pattern-sensitivity and television fits was significant. Of these 17 patients, 10 were sensitive to static and moving patterns and, in the other 7 cases, spike and wave was evoked only by the vibratory display.

Comparing the efficiency of two stroboscopes, one of which had a fine metal wire guard over the screen, Jeavons et al. (1972b) discovered, by chance, that the latter stroboscope raised the incidence of a PCR without any increase in the stimulus intensity. Subsequently, a detailed study of 10 patients showed that at a low intensity no PCRs were evoked using a plain glass or diffusing screen and only one patient responsed to a large squared pattern consisting of thick black lines subtending 34' of visual angle and being 34' apart. Horizontal and vertical lines produced spike and wave in 5 and 6 patients respectively at this low intensity, whereas the metal grid evoked a PCR in 9 patients. All 10 patients reacted to a small black grid pattern with squares subtending 22' visual angle.

Engel (1974) disputed these findings. He found that 12 out of 28 photosensitive patients showed a differential sensitivity to plain diffused flash and a patterned flash of 20' black and white checkerboards. Sensitivity to only diffuse flash occurred in 7 patients, 16 were sensitive to plain and patterned flash and 5 reacted to patterned flash only. He concluded that patterned flash stimulation was not necessarily better than diffuse flash for evoking PCRs and that the routine use of only patterned IPS would fail to detect a certain percentage of photosensitive patients. However, Engel made no

correction for intensity during patterned stimulation and Jeavons and Harding (1975) commented that a checkerboard pattern effectively halves the intensity of the diffuse flash. These authors postulated a close connection between pattern-sensitive and photosensitive epilepsy in that similar mechanisms might be operating in the former to those which potentiate the effect of patterned IPS; the difference being that light is more potent in photosensitive epilepsy than patterns alone, and vice-versa for pattern-sensitive epilepsy.

Pattern-sensitive epilepsy is a rare disorder (Chatrian et al. 1970a) but it has been noted that the majority of cases are reported as also being photosensitive (Wilkins, Andermann and Ives 1975). Laboratory studies on the triggering effects of pattern itself or in combination with IPS, have shown that the optimum stimulus contains fine geometric elements in the region of 11' - 24' subtense (Chatrian et al. 1970a; Jeavons et al. 1972b; Wilkins et al. 1975). Research on patterned-flash and pattern-reversal visual evoked potentials have shown that maximal amplitudes are obtained with pattern elements of 10' - 30' visual angle (Eason, White and Bartlett, 1970; Harter and White 1970; Cigánek 1971; May, Forbes and Piantanida 1971; White 1974). This indicates that the visual cortex plays a major role in the triggering mechanisms of pattern and authors have implicated the differential effects of visual receptive cells. Complex and hypercomplex receptive cells, as found in cat and monkey visual cortex, respond to contrast and contour. In primates slits, bars and edges of critical width, angle and orientation fire these line-detectors (Hubel and Wiesel 1959; 1962; 1968). Changing the orientation of more than 5^{o} - 10^{o} is enough to abolish unit responses (Chatrian et al. 1970a).

Pattern-stimuli are not totally static owing to fine eye movements (Darby et al. 1977). Troupin (1966) reported on the effectiveness of pattern in the production of a PCR. As in some cases it was unnecessary to flash or move the pattern, he considered the triggering effect to be due to spatial alternation of the stimulus, as opposed to temporal alternation during IPS. Wilkins et al.(1975) termed this 'quasi-photic stimulation' caused by eye nystagmus over the pattern. Some patients are, however, sensitive to orientation of pattern, e.g. vertical lines as opposed to horizontal or angled lines (Bickford and Klass 1969). Nystagmus is usually omnidirectional and in the absence of a definite astigmatism the quasi-photic stimulation theory is unfounded (Wilkins et al. 1975). The answer may again lie in the cortical cells. The monkey has no predominance of cells that show orientational effects but this would correspond with its environment as it does not live in an 'upright world'. Kittens visually deprived except for vertical and horizontal contours will only develop visual cortical cells responding to these shapes. Man is an upright animal and lives in a world full of vertical and horizontal contourd (Yoshida, Iwahara and Nagamura 1975). It may be, therefore, that human cells are more responsive to the principal meridians, which influence the cortical component of the pattern-sensitive response.

2.6. The Visual Evoked Potential.

The EEG can be considered as a mixture of signals fluctuating widely in frequency, amplitude and phase as a result of diverse neural activity in the brain. Within this sea of activity the response to a discrete stimulus may be detected from the assumption that the evoked response will be time-locked to the stimulus whereas the background EEG will be random and unrelated (Harding 1974). These evoked potentials are however, usually small in comparison to the spontaneous EEG activity and so techniques of superimposition and averaging of the responses (Dawson 1951) have been developed. Averaging techniques depend on increasing the signal to noise ratio which improves by the square root of the number of responses. The time-locked response is summated and appears to crystallise out of the EEG as the unrelated ongoing positive and negative waves summate to zero.

Transient visual stimulation,viz. a flashing light produces a cerebral response, maximally recorded in the occipital region, called the visual evoked potential (VEP). It can be displayed by the above techniques as a plot of amplitude against time (Harding 1974) and is seen as a complex polyphasic potential of alternating polarity (Černáček and Cigánek 1962; Rietveld 1963). The total duration of the VEP is about 250 - 300 msec. (Van Hof 1960; Rietveld 1963). Detailed reviews of the VEP can be found in Van Hof (1960); Rietveld (1963); Bergamini and Bergamasco (1967); Harding (1974).

An inherent assumption of evoked response recording is that the background EEG has no influence on the actual response to the incoming stimulus (Harding 1974). However,

this is not strictly true. Adrian and Matthews (1934) believed that the rhythmical occipital response to flashing light was 'driving' of the spontaneous alpha rhythm. Later, the connection between these two phenomena was considered to be superficial by Walter et al. (1946), although they believed an intricate relationship existed between them. The pattern of alpha activity was found to predict the stability of the entire EEG by locking together the activity from all cortical areas (Ulett and Johnson 1958). They suggested that alpha had a fundamental role in the organisation of visual activity. The variability of the VEP was reported as being due to the background EEG on which these responses were superimposed (Cobb and Dawson 1960; Cigánek 1969). However, there is disagreement as to the differential effect of EEG activity on individual VEP components. The after-discharge, a sinusoidal rhythm occurring at 300 msec. and only present during eyes-closed recording, has been related to the frequency of the alpha rhythm (Rietveld 1963; Beck and Dustman 1975), whereas Kooi and Bagchi (1964) reported that the amplitude variations of all components between 80 - 140 msec. of the eyes-open flash VEP, tended to parallel those of the resting alpha rhythm. The latency of the negative 80 - 110 msec. component was inversely related to alpha frequency. Callaway and Buchsbaum (1965) found VEP variation in relation to which phase of the cardiac or respiratory cycle IPS was presented.

In man marked inter-variability of VEP amplitude occurs. Besides the controversial effects of the background EEG, differences in stimulus parameters viz. intensity, frequency, pattern, eye-states, age, wakefulness and sleep, variation in the 'internal mileu', pupillary size, habituation

to prolonged stimulation and even skull thickness and head shape contribute to real or minor variations in the morphology of the averaged VEP (Ebe, Mikami, Ito, Aki and Miyazaki 1963; Rietveld 1963; Cigánek 1969; Dustman and Beck 1969; Lehtonen 1973; Buchsbaum 1974). To maximise the efficiency of the recording situation and to remove artefacts like muscle activity or eye-blinks it is essential to relax and encourage co-operation from the subject (Harding 1974).

Fig. 2.1. shows the morphology and terminology of VEP components by various authors, as recorded by a flashing light with frequencies up to 3 c.p.s.. Despite inconsistencies in recording methods the VEPs reported in the literature are comparable; although confusion can arise as some authors number peaks and troughs without stipulating their polarity. Harding (1974) recommends the use of an N or P prefix to denote negativity or positivity respectively. Recent recommendations support this view, although proposing a latency rather than a numerical subscript (Desmedt 1977).

Cobb and Dawson (1960) observed that the initial VEP component was positive with a 20 - 25 msec. delay and that the electroretinogram (ERG) recorded at the eye was independent of any VEP component. Other authors have failed to detect the initial positivity. Černáček and Cigánek (1962) believed that the first deflection was negative going at 28 - 30 msec. but Lehtonen (1973) supported Cobb and Dawson's initial finding. The most prominent and consistent component of the VEP is the major positive component occurring between 100 - 120 msec. (Harding 1974).

The VEP undergoes latency and ampitude alterations with age development. Walter et al. (1946) observed that children up to 12 - 14 years and young adults had relatively

	I	II	III	IV	V	VI	VII	Ciganek 1961
1	2	3	4	5	6			Ebe et al. 1963
1	2	3	4	5	6			Gastaut and Regis 1967
	A	B	C	D	E	F	G	Dustman and Beck 1969
	N_1	P_1	N_2	P_2	N_3	P_3		Lehtonen 1973
P_0	N_1	P_1	N_2	P_2	N_3	P_3	N_4	Harding 1974

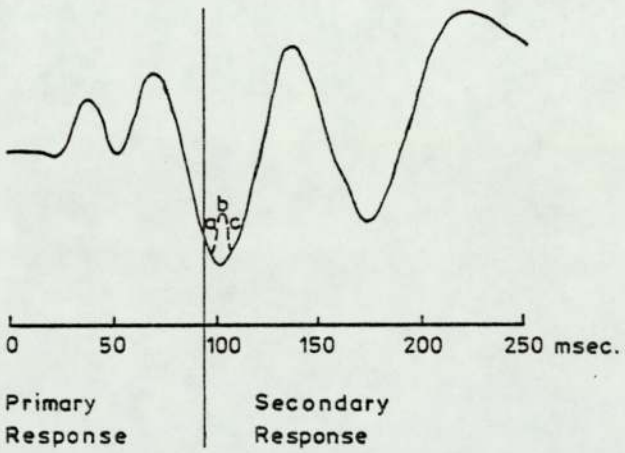


Fig. 2.1. Profile of the Visual Evoked Potential (adapted from Harding 1974)

large responses to flash at frequencies up to 6 f.p.s.. Dustman and Beck (1969) observed a rapid increase in ampitude reaching a maximum at 5 - 6 years with a decline from 7 - 13 years. An abrupt increase occurred again at 13 - 14 years. The occipital responses became more individualised with age, reaching a peak at 16 - 17 years with a concomitant stabilisation in ampitude (Beck and Dustman 1975). They concluded that there appeared to be a differential development in the various brain regions with the occipital VEP becoming less uniform and the central response more uniform. At young adulthood the homogeny of each area was roughly equal.

Although the VEP phase reverses and is generally maximal at the occipital electrodes, vertex sharp waves can be detected in the central region with the same latency as the late negative potential (N3) of the occipital VEP. Kooi and Bagchi (1964) found that the vertex sharp wave did not vary in relation to the ampitude, frequency, or incidence of the resting alpha rhythm unlike components of the occipital VEP. Using a contoured pattern flash, Lehtonen (1973) postulated that the apparently similar vertex sharp wave and late VEP deflections represented different neurophysiological phenomena. The occipital deflections probably reflected cortical modality - specific functions and vertex sharp waves non-specific functions.

There has been a great deal of argument as to the origin and meaning of the VEP components. Cigánek (1961) labelled the first 3 waves between 0 - 90 msec. as the 'primary response' and components between 90 - 240 msec. the 'secondary response' (Fig. 2.1.). The 'primary response' was believed to originate in area 17 of the striate visual cortex after following a specific pathway through the geniculate

bodies. This conclusion was based on its short latencies, relative consistency, resistance to increasing flash rate, and resistance to sleep. The 'secondary response' however, was considered as non-specific and arising in diffuse polysensory thalamic pathways due to its long latencies, suppression by increasing flash frequencies, and marked alteration by both stimulus and subjective variations, viz. level of arousal and attention (Cigánek 1961; Bergamini and Bergamasco 1967; Beck and Dustman 1975).

Evoked potentials are thought to be the summation of synchronous excitatory post-synaptic potentials (EPSPs) and inhibitory post-synaptic potentials (IPSPs) of cortical and possibly glial cells plus synchronous afferent and efferent nerve fibre activity (Creutzfeldt and Kuhnt 1967; Arden 1973). Thalamic afferents are believed to terminate in the fourth layer of the striate cortex, producing the first cortical synaptic connection which amplifies the signal and is finally passed through pyramidal cells to the fifth and sixth layers. This polysynaptic depolarisation, registered as a positive wave at the cortical surface, spreads through apical dendrites just beneath the surface and becomes inverted giving rise to a negative surface wave (Bergamini and Bergamasco 1967). This is a much simplified explanation and in the case of the VEP pre- and postsynaptic parts can be detected, the former corresponding to the arrival of afferent impulses from the lateral geniculate body and seen as the first three waves of the response. After this primary excitation, from electrical stimulation of the specific afferents, IPSPs ensue as reflected in the major positive component (Creutzfeldt and Kuhnt 1967). These authors report that in the visual cortex many cells show an IPSP

without a preceding EPSP and that such inhibition is only evoked through intracortical recurrent collaterals and not directly from thalamo-cortical afferents. Their model of evoked potential electrogenesis does not assume discrete and different generators in the cortex but that phase reversal of the potential, using bipolar recording techniques, may result from changes in potential difference along vertically orientated cells. They hypothesise that in the human VEP, the negative components represent an excitation of most cortical cells and that a polarisation (inhibition) forms the major positive (P_2) and last positive (P_3) components. The late negative wave (N_3) is considered to be a late 'non-specific excitation' superimposed on the long-lasting IPSP.

2.6.1. The VEP in epilepsy.

Černáček and Cigánek (1962) recorded the averaged occipital VEP from 30 epileptics with varying types of seizures. Comparison with a normal group showed that the early waves, in particular wave 111 (Fig.2.1.), were lower in amplitude. Later waves however, were increased. Reduction of the 'primary response' in the epileptics was also evident as diminished photic driving at 16 f.p.s.. As this effect was apparent in untreated patients and those on anticonvulsants, they attributed it to the epileptic condition, whereas they assumed the increased 'secondary response' was the result of medication. Large amplitude VEPs, mainly due to increased late components, were also observed by Crighel, Rosianu, Constantinescu and Matei (1974) in a mixed epileptic group. A study of patients with centrencephalic epilepsy showed that in addition to ample late waves, the after discharge was also of higher amplitude and of longer duration (Bergamini and Bergamasco 1967). Needham, Dustman, Bray and Beck (1971)

supported findings of raised amplitudes but only in relation to the area of VEP recording. The amplitude of both early and late waves of centrally derived responses were significantly larger in epileptics but occipital VEPs were not found to differ from those of normals. Conversely, Lücking, Creutzfeldt and Heinemann (1970) observed that the maximum amplitude of the VEP was depressed in central and temporal regions and suggested that the spread of VEP activity into non-visual areas, especially the vertex, was reduced in epilepsy.

Several authors have reported that the epileptic VEP is more variable than seen in the normal population (Lücking et al. 1970; Crighel et al. 1974). However, in these particular studies added variation may have arisen from the inclusion of epileptic samples with a wider age range than the control groups. Differences in the state of the basic EEG during recording and the use of clinically different patients may also contribute to the overall variability.

The VEPs of patients with spike and wave discharges have been found to be more variable and more abnormal than those of patients with normal EEGs. In fact the VEPs in this latter group were similar to those of control subjects. In the paroxysmal patients no single component showed a consistent alteration but the entire VEP tended to be irregular (Crighel et al. 1974). No correlation was found between the VEP and different types of EEG abnormality but the most marked EEG alterations occurred in those epileptic patients who underwent changes in the level of awareness, and it was this group who showed a higher incidence of abnormal and variable VEPs. The VEPs of close relatives had the same high amplitude characteristics as the epileptics, even though their EEGs were normal. Patients with focal epilepsy, although

possessing significantly larger somato-sensory potentials (SEPs) than healthy normals, showed no consistent differences in their VEPs as regards amplitude, morphology or distribution (Bacia and Reid 1967). A comparison between homologous temporal areas in patients with temporal lobe epilepsy and unilateral EEG changes showed no differences in the VEPs recorded in each hemisphere.

Finding that the 'primary response' was diminished in epileptics, Černáček and Cigánek (1962) proposed that in different types of epilepsy significant depression of the specific optic pathway occurs but were uncertain as to its extent within the visual cortex. The fact that VEPs were recordable during generalised seizures (Rodin, Gonzales, Caldwell and Laginess 1966) and even during the clonic slow wave phase, suggested that active inhibition was not the most probable cause for the transition to this activity but, if inhibition did occur, not all cortical neurons were participating. Others have proposed the existence of differing but linked mechanisms for the regularity of the EEG and the VEP (Lücking et al. 1970; Needham et al. 1971). Due to the large and persistent after-discharge in epileptics, Bergamini and Bergamasco (1967) believed it represented a prolonged and greater excitation of the resonating autorhythmic circuits. Ebe et al. (1963), finding shorter latencies and increased amplitudes in all VEP components, particularly for tonic-clonic patients when compared to matched controls, contributed it to increased cerebral excitability.

2.6.2. The photosensitive VEP and occipital spikes.

Examining the eyes-open VEP in occipital, parietal and central regions of two pattern-sensitive epileptics, Chatrian et al. (1970b) found normal responses in the absence

of background spike and wave discharge. During paroxysmal activity the early components were replaced by a single negative wave, but the most consistent component still occurred around 100 msec.. These findings support Rodin et al. 1966.. The VEPs of two patients with 'photogenic epilepsy' were found to follow the same trend as other epileptics VEPs (Černáček and Cigánek 1962). Bablouzian et al. (1969) found that even in photosensitive patients with normal EEGs the eyes-closed VEP was larger than normally seen. The latency of the first peak occurred earlier, at 35 msec. and the highest peak was twice as large with a longer delay (183 msec.) than control subjects. A few other photosensitive patients were reported as having abnormally large occipital VEPs (Lücking et al. 1970; Crighel et al. 1974).

Andermann et al. (1962) comparing the latencies of spikes obtained with single flashes believed that the major component might represent a pathological exaggeration of the second positive wave of the evoked potential. Morphologically similar VEPs were obtained for photosensitive and normal subjects (Hishikawa et al. 1967). However, certain conponents in the VEP of photosensitives were larger and the overall recovery cycle shorter. In 8 patients whose PCRs were initiated in the occipital region, 6 showed repetitive occipital spikes induced by a series of flashes and occurring at the same rate as the flash. Following spikes had the same or slightly longer latencies than the initial spike. Comparing occipital spike latencies from single, double, and trains of flashes with the VEP components of normals, the authors postulated that the occipital spike was either an enhanced N2, of mean latency 45 msec., or N3 at 88 msec..

Gastaut and Régis (1964) also reported the augmentation of selective VEP components in photosensitives. In particular wave V (P_2) at 140 msec. was often triphasic with a positive Va, negative Vb, and positive Vc component. The characteristic feature was that Vb increased in amplitude until it exceeded all other components. Facilation of Vb was very marked during seizures and became diminished during seizure reduction either spontaneously or by anticonvulsants. In a group of young patients with myoclonic epilepsy the VEP was modified only when IPS evoked polyspike and wave discharges. Overall amplitude was increased but in particular Gastaut's Vb component. Again, facilation of this wave was even greater during myoclonic seizures (Bergamini and Bergamasco 1967). Other authors have drawn comparisons between their findings and the triphasic V wave. Broughton et al. (1969) reported a similar component in the eyes-closed VEP, with a positivity at 124 msec., negativity at 140 msec., and following positivity at 194 msec.. In photosensitive patients this negative polarity was increased and of longer latency. The authors, also finding selective increases in amplitude, disputed others' findings of diminished early components or entirely larger VEPs. Green (1969) believed that a positivity between 60 - 115 msec. in the VEP of his photosensitives represented the Va component. Seizure discharge and eye-closure enhanced the amplitude of this wave whereas monocular occlusion reduced the VEP and EEG abmormality.

Panayiotopoulos et al. (1970; 1972) recorded VEPs in photosensitive epileptics using a fine grid pattern at 1 - 4 f.p.s. with eyes-open and compared the latencies with components and occipital spikes seen at 5 - 9 f.p.s.. The spikes were triphasic with an initial positivity between

76 - 99 msec. and a major negative component between 94 - 118 msec. that phase reversed with maximal amplitude (60 - 100 + μv.) at the occipit. Occipital spikes tended to increase in amplitude with increase in flash rate and, in a few cases, a longer latency occurred (up to 15 msec.) with this enhancement. In other cases the latency remained unchanged even when the interstimulus interval was shorter than the latency of the negative peak. The latency of the subsequent positive wave was found to be inconsistent at higher flash frequencies. The authors considered that when interstimulus intervals were very short the occipital spike was in fact the response to the preceeding flash but one, and had not shown a marked reduction in latency. This would also explain the latency variations reported by Hishikawa et al. (1967). At 1 - 4 f.p.s. the mean latencies of N2 and P2 were 79 and 110 msec. respectively. The authors found, therefore, no augmentation of the negative VEP components in producing the occipital spike. However, in 50% of the patients the latency of the negative spike coincided with the latency of the P2 component. In two patients there was a definite relationship between the occipital spike and the P2b component of a triphasic P2. In one patient P2b clearly grew into the occipital spike with increasing flash rate.

Under similar recording conditions Dimitrakoudi, Harding and Jeavons (1973) reported that the occipital spike was a constant feature associated with the VEP of photosensitives. Of 46 patients, 31 had occipital spikes visible in the EEG and in 42 they were present in the VEP. The mean latency of the N2 component was 58 msec. and for P2, 111 msec.. The negative polarity of the occipital spike occurred with an average latency of 91 msec. and tended to

appear on the descending phase of P2. The latencies of P2 and the occipital spikes were consistent for each patient irrespective of the flash rate. In 26 patients occipital spikes were observed in the VEP at 1 f.p.s. and the authors considered this due to the provocative grid patterned stimulus. Removing the grid suppressed and sometimes abolished the occipital spike. Similarly, monocular stimulation markedly reduced the amplitude of the occipital spike in the VEP and often it was no longer visible in the EEG. Jeavons and Harding (1975) believe that the occipital spike is related to the P2b component, particularly apparent in the VEP of photosensitives, as suggested by Gastaut and Régis (1964).

The P2 component or V wave has been implicated with foveal functioning. The Va component was seen to decrease in amplitude under dark adaptation with eyes-closed and the amplitude of Vc increased. This suggested that Va was related to photopic systems and so associated with cone activity in the rod-free fovea. Conversely, the Vc component was linked to scotopic functioning of the peripheral retinal rods (Gastaut, Orfanos, Poiré, Régis, Saier and Tassinari 1966). As P2 is the most consistent and distinct VEP component and can be seen in the EEG of some individuals, it is thought to represent occipital lambda waves. Lambda waves are positive cortical potentials, occasionally observed at eye-opening, but mainly with scanning movements across a patterned field causing a shift in macula vision (Evans 1953; Gastaut and Régis 1964; Scott, Hoffman and Bickford 1967). In a mixed clinical group no significant difference was found for age, sex or diagnosis between lambda and non-lambda groups (Jaffe and Dipmore 1975). No significant connection between the occurrence of EEG lambda waves and epileptiform

discharge in pattern-sensitive epileptics was found by Chatrian et al. (1970b). However, Evans (1953) had previously reported that a correlation existed between lambda and the ability of IPS to evoke EEG abnormality, particularly at low flash rates.

Cortical projection of the macular is relatively more extensive than that of the peripheral retina (Chatrian et al. 1970b; Regan, 1972). If P2 represents macular function and the occipital spike is related to P2 it follows that the majority of cortical cells will be influencing the appearance of the occipital spike. Jeavons and Harding (1975) state that the high incidence of occipital spikes in their studies was due to the combination of a high intensity, diffused light and finely patterned stimulus which would optimally involve the Hubel and Wiesel type cells in the cortex. Also, closing the eyes, monocular occlusion, plain diffused or blue light reduces cortical stimulation and suppresses the occipital spike. Creutzfeldt and Kuhnt (1967) have postulated that the cortical VEP was principally the culmination of IPSPs. However, at flash rates above 5 - 10 f.p.s. IPSPs diminish and will disappear completely by 10 - 15 f.p.s. (Kuhnt and Creutzfeldt 1971). This reduction is also accompanied by a release of EPSPs. They proposed, therefore, that this might increase the excitability of the cortex and noted that 8 - 15 f.p.s. is effective in evoking paroxysmal activity in some epileptics. Jeavons and Harding (1975) interpret the occipital spike as a failure of normal inhibitory mechanisms, and when occipital spikes are seen to be precursors of the PCR propose that IPS provokes a focal occipital abnormality through summation of excitatory potentials which then triggers a secondary generalised discharge.

2.7. Sleep Studies.

The photosensitive threshold was found to be raised during spontaneous sleep and even more so during premedicated sleep (Rodin, Daly and Bickford 1955). Photosensitivity was abolished in 43% of patients and the remainder showed less IPS induced abnormality than compared to their waking state. Hishikawa et al. (1967) could not evoke spike and wave discharges during light or deep sleep even with prolonged IPS. PCRs similar to those occurring during wakefulness were clearly evoked during REM sleep. However, a marked decrease in the PCR and PMR was found during non-REM and they were even more reduced or disappeared during the REM phase (Meier-Ewert and Broughton 1967; Broughton et al. 1969). These authors found that sleep had a differential effect upon spontaneous and evoked abnormality. During the non-REM stages spontaneous polyspikes, polyspike and wave and 3 c.p.s. spike and wave bursts could still be visible and appeared to grow out of the sleep spindles. No spontaneous discharges occurred during REM sleep. Diminished photosensitivity was still seen during arousal from non-REM sleep, although assessment was difficult due to prolonged generalised myoclonic episodes. However, within 10 minutes of arousal from REM sleep there was a rapid return to pre-sleep levels of photosensitivity and no spontaneous myoclonic discharges. Similar fundings were reported by Scollo-Lavizzari and Hess (1967). They noted that in comparison to focal epilepsies, where EEG changes are activated in all sleep stages, IPS was an ineffective trigger in photosensitive centrencephalic epilepsies. However, sleep deprivation for up to 36 hours provoked or increased the photosensitive response even after a short, notably deep sleep period (Scollo-Lavizzari and Scollo-Lavizzari 1974).

This was considered to be mainly due to REM sleep deprivation producing neuronal hyperexcitability. No correlation was found between blood glucose levels, pupil dilation, and photosensitivity. REM is associated with a small build up of monoamine in the pons nuclei and animals deprived of REM show a 50% reduction in the electroshock threshold.

The normal VEP during drowsiness and light sleep is reported as being similar to that recorded in wakefulness. During deep sleep however, the early components were seen to diminish, in particular N2, and the later parts to predominate with a positive - negative - positive polarity of 65 - 110 - 250 msec. mean peak latencies. The morphology, latencies and distribution became similar to those of the k-complex (Bergamini and Bergamasco 1967). The REM phase VEP was of the same waveform as the awake VEP but smaller in amplitude. The VEP in photosensitive epilepsy was reported to undergo a similar transformation of increased latency and reduced amplitude of early waves with an appearance of the large triphasic wave of 70 - 80 msec. positivity, 100 - 200 msec. negativity and a following positivity at 180 - 260 msec.. The after-rhythm disappeared and was often replaced by 12 - 15 c.p.s. spindle activity. The occipital VEP during REM sleep showed unaltered latencies and amplitudes of the early components. Later components reappeared but were slightly delayed. No after-discharge was present (Broughton et al. 1969).

3. THERAPY

3.1. Conditioning.

Forster and his colleagues were the first authors to report on conditioning as a therapeutic method in photosensitive epilepsy (Forster and Campos 1964; Forster et al. 1965). Their patients varied as regards clinical seizures, photic precipitation, age range and I.Q. However, stroboscopic light produced EEG abnormality in all patients and in no case was there an island of insensitivity within the critical frequency range. Three methods of extinction were used. The first method was based on the principle of reduction in photosensitivity by monocular stimulation. After determining the patient's binocular sensitivity range and whether monocular occlusion, using an eye patch, inhibited the spike and wave abnormality, a series of extinction trials ensued with repeated photic stimulation around 21-22 f.p.s. given to one eye and then to the other. Back-up trials could be conducted at home by adjusting the television to flop over at about the same frequency as that used in laboratory stimulation. The rationale behind this method was that repeated trials would inhibit cortical hypersynchrony and thus clinical seizures due to binocular stimulation. Although the authors reported success in 4 out of 5 patients, the techniques proved laborious as extinction trials were required at each frequency of the sensitivity range. Braham (1967) reported complete failure of this method and indicated increased photosensitivity in one patient after two weeks of repeated extinction trials. In fact, Forster et al. (1965) mentioned the possibility of making the photosensitive condition worse by 'errors in

techniques'. It was not only possible to reverse the extinction process but there was also a danger of the patient's condition deteriorating. Self-inducing photosensitive epileptics were the most difficult patients to treat using this method (Forster et al. 1965). Monocular conditioning therapy is of limited value when considering that patients with abnormal basic EEGs generally show greater sensitivity to monocular stimulation (Jeavons et al. 1966).

The second conditioning technique required determination of the lower and upper limits of the binocular sensitivity range and then presentation of a series of stimulations at a safe frequency just outside the range. If no abnormality occurred, the extinction trials were repeated by encroaching onto the sensitivity range limits. This method was found to be difficult and time-consuming.

The third procedure employed differential light intensity. An opaque glass screen was placed in front of the photo-stimulator, on either side of which was placed a reflecting photoflood bulb. A rheostat controlled the brightness of these bulbs, which was set at an intensity so that no EEG abnormality occurred during IPS. In this way repeated extinction trials were administered and subsequently repeated with successive reductions in the brightness of the photoflood bulbs. This method was tenable as the contrast between flicker and background illumination has a fundamental influence on photosensitive responses. The authors found this method the most effective and the simplest of all three. However, as with the first method, it is applicable to a particular flash rate and so the other flash rates in the range would require extinction trials. Also the effect was

not permanent and day-to-day back-up trials in the home were difficult to devise.

Forster (1967) later adapted the third method of extinction to treat eye-closure induced epilepsy in one patient. Eye blinking in the dark did not produce EEG alteration as seen in the light. The patient blinked repeatedly in the dark for one hour, during which time light was introduced gradually. Finally, blinking in full light failed to produce EEG abnormality.

All three extinction methods failed when tested by Harding et al. (1969), thus supporting Braham (1967). The rationale behind conditioning techniques as a therapeutic means was based directly on Pavlov's theories in that, at the beginning of a series, a greater number of extinction trials were required for a slight improvement and a lesser number for a marked improvement at the end of the study; there was a specificity of extinction for a particular flash rate in that the patient remained sensitive at other frequencies; partial decay of extinction occurred, although the effect was not permanent, (Forster and Campos 1964). Also on theoretical grounds Jeavons and Harding (1975) argued the implausibility of these conditioning methods. It may be possible that IPS (the unconditioned stimulus) could become associated with a conditioned stimulus (e.g. a bell) to such an extent that the latter alone may produce a PCR (the response). However, the unconditional stimulus, IPS, cannot be extinguished even when it is possible to extinguish the association of a conditional stimulus (e.g. bell). Extinction of the unconditional stimulus is not supported by conditioning therapy. Therefore, for conditioning therapy

to be successful in photosensitive epilepsy, the conditional stimulus would need to be the flickering light in association with an unknown unconditional stimulus.

3.2. Monocular Occlusion.

The effect of monocular stimulation on photosensitivity has been frequently described in the literature since Bickford et al. (1952) reported total inhibition of the PMR through monocular stimulation. A PCR, however, could still be elicited. Later Marshall et al. (1953), describing a case report, found that during monocular stimulation the light intensity had to be doubled in order to produce a PCR. Increased photosensitive threshold occurring with monocular stimulation (Brausch and Ferguson 1965) has since been corroborated by many authors (see Section 2.4.1.). Green (1966) explained this effect as being due to interference with binocular vision and convergence mechanisms, besides a reduction in the amount of stimulation, and suggested the wearing of an eye patch as a therapy. Eye-closure is another complicating factor in photosensitivity (see Section 2.4.2.). Spike and wave abnormality in the basic EEG following eye-closure usually indicates that IPS will evoke paroxysmal discharges (Jeavons 1969). Also there is a tendency for patients with spontaneous EEG abnormalities to show a greater response to IPS and more sensitivity to monocular stimulation than patients with normal basic records (Jeavons et al. 1966). Green (1966) believed that an eye patch would reduce blinking and thus improve spike and wave in the EEG as a result of reduced brain hyperactivity. No photosensitive paroxysms occurred in more than 50% of patients during monocular stimulation (Jeavons 1969) and subsequently monocular occlusion was reported as an effective therapy with 'television epilepsy' (Jeavons and Harding 1970). These authors particularly advised patients who were impul-

sively attracted to the television to wear a lightproof eye-patch. Although this benefited the condition, young patients were particularly unreliable in wearing the patch. A child would not tolerate an eye patch if he would not cover his eye with his hand. Eye-patch therapy has therefore met with varying success (Green 1966, Jeavons and Harding 1975). An easier remedy was to advise patients sensitive to television and other environmental light stimulation, when experiencing pre-seizure symptoms, to cover one eye immediately with the hand (Hess et al. 1974). This method of monocular occlusion is effective when the palm is pressed firmly over the eye and close to the edge of the nose (Jeavons and Harding 1975).

Monocular occlusion using frosted spectacles has been used in the case of a girl who suffered EEG paroxysms and clinical absences when viewing striped patterns (Wilkins et al. 1975). Pattern vision was occluded in the upper and lower visual field, the occluded eye being changed each day for a week. EEG cassette recordings showed more than an 80% reduction in spike and wave discharges, with accompanying improvement in attention and arousal. The authors claim that the beneficial effects of this therapy far outweigh any improvement through prolonged monocular occlusion. However, Zubeck and Bross (1972) investigating the critical fusion frequency (CFF) in normals have shown that prolonged monocular occlusion may initially produce a depression of the CFF in the non-occluded eye but that afterwards a reversal occurs between 6 to 9 hours followed by an enhancement effect up to 24 hours. No change occurred in the occluded eye. This reaction was independent

of whether the dominant or non-dominant eye was covered. The authors believed that prolonged monocular deprivation could produce changes in primary sensory areas comparable to denervation supersensitivity which occurs in the higher neural centres after partial surgical deafferention at lower levels of the CNS; supersensitivity being a compensatory process occurring as a consequence of basic sustained change in the level of input to an excitable structure. Although the flicker stimulus of Zubeck and Bross (1972) differs from the pattern stimulus of Wilkins et al. (1975) monocular occlusion for a whole day is within the time period for reversal and enhancement of response as described by the former authors. This finding may also bear some relation to the failure of monocular conditioning techniques of photic stimulation.

3.3. Spectacles.

Early literature showed that decreasing the intensity of photic stimulation would reduce its ability to evoke paroxysmal discharges (Goodkind 1936; Bickford et al. 1952; Bickford and Klass 1969). Tinted or polaroid spectacles have been recommended by several authors (Bickford et al. 1953; Ganglberger and Cvetko 1956; Wadlington and Riley 1965). Neutral tinted glasses or contact lenses reduce the intensity of a flickering light source. Another potential hazard in the environment is reflected sunlight on rippling water, reflections on the leaves of trees or from car windscreens (Cobb 1947; Jeavons and Harding 1975). Polarising glasses eliminate these specular reflections (Hess et al. 1974) and by adjusting the rotation of the polarising lenses the transmitted light can be controlled according to the environmental illumination (Bickford et al. 1953).

Research into the effect of coloured light on photosensitivity suggests that red light stimulation can cause a definite increase in the photosensitive response (Carterette and Symmes 1952; Marshall et al. 1953; Pantelakis et al. 1962; Brausch and Ferguson 1965; Capron 1966). The wearing of spectacles with red filtering lenses by photosensitive patients was proposed by Carterette and Symmes (1952), Bickford and Klass (1969) also reporting on the wearing of minus-red glasses noted occasional elimination of red sensitivity. However, the varying success of these coloured spectacles has often been shown to be due more to a reduction in the intensity of the light stimulation through the use of very dense coloured filters (Troupin 1966).

Forster et al. (1965), still pursuing conditioning therapies, developed spectacles for a female patient with marked photosensitivity and associated clinical absences which at times were self-induced. A photocell in the glasses picked up selective flicker which was relayed through a modified hearing aid to produce audible clicks. The authors claim that the patient's seizure rate was dramatically reduced and while it was still possible to evoke spike and wave under laboratory conditions it was much less frequent than before the extinction trial. However, the patient's sensitivity varied with her menstrual cycle and her clinical seizures were aggravated by tension and fatigue. The authors do not say if the effect of menstrual cycle was controlled for before and after extinction trials.

Pattern is a complicating factor in the precipitation of a photic response and so Chatrian et al. (1970b) investigated the wearing of glasses with spherical diopters (usually +3). Lined patterns became blurred when viewed through the lenses but after lengthy wearing the glasses completely lost their protective effect due to the patient learning to relax his accommodation at near vision.

The most objective experiments with protecting spectacles were reported by Harding et al. (1969) and Jeavons and Harding (1975). Although polarising lenses proved more effective than tinted glasses, probably due to adaptation at low levels of intensity through pupil dilation, polarising glasses did not protect against direct flicker. Spectacles were therefore devised to recognise flicker in the environment, control against the intensity of sunlight as it became brighter and to eliminate reflected flicker. A photo-

cell connected to a filter circuit registered environmental flicker. If this was within the patient's sensitivity range, small light bulbs set in prisms reflected a steady light source onto the retina at a visual angle of 20^{o} depending on pupil size. The rationale of these spectacles was to reduce the apparent contrast between the flickering light source and surrounding environmental illumination. The spectacle lens consisted of a photosensitive absorptive filter, a polarising filter and an optical correction film. This lens reduced brightness of sunlight but allowed comfortable television viewing, removed specular reflections and adjusted the patient's refractive error. The spectacle frame also had wide photosensitive absorptive side panels to attenuate oblique light. Tests using the anti-flicker spectacles inhibited the PCR in 10 patients using the normal length of stimulation and also prolonged IPS. However, the spectacles were never generally produced for day-to-day wearing. Covering one eye was found to be effective in most patients in controlling attacks which exaggerated the cost of producing special glasses which were not particularly attractive cosmetically. Nevertheless, the authors still recommended the photochromic layer and polarising layer as a useful therapy for patients sensitive to external illumination, viz. passing from a dark room into bright sunlight.

3.4. Biofeedback.

The management of epilepsy using biofeedback of EEG rhythms is a relatively new concept. Preliminary studies with rats showed the presence of a 12-16 c.p.s. rhythm over the sensorimotor cortex during voluntary suppression of movement. The rhythm was therefore called Sensorimotor Rhythm (SMR), and was found to originate in animals in the ventrobasal nuclei (Sterman 1973). Biofeedback of this activity by operant conditioning caused modified sleep in cats but more impressively increased the resistance to drug induced seizures (Sterman 1973). This author considered SMR to represent a type of 'cortical idling' in association with inhibition of motor activity and that increasing this idling through operant conditioning might block overt epileptic activity. SMR in humans is seen as the sleep spindle but during wakefulness detection usually requires frequency filtering from rhythms in the rolandic area. It is of low amplitude (5-15 μV), and its detection is not always inhibited by small, localised movements (Sterman 1973; Sterman, Macdonald and Stone 1974; Seifert and Lubar 1975).

Biofeedback procedure involves the operant condition of a selected EEG rhythm, in the absence of EEG epileptiform activity, when it reaches predetermined criteria for percentage time of occurrence and amplitude. Fig. 3.1. shows the basic type of circuitry that controls the operant stimulus. In most studies the signal is transformed to an auditory or visual display involving various reward systems (Sterman 1973; Sterman et al. 1974; Seifert and Lubar 1975; Lubar and Bahler 1976; Wyler, Lockard, Ward and Finch 1976).

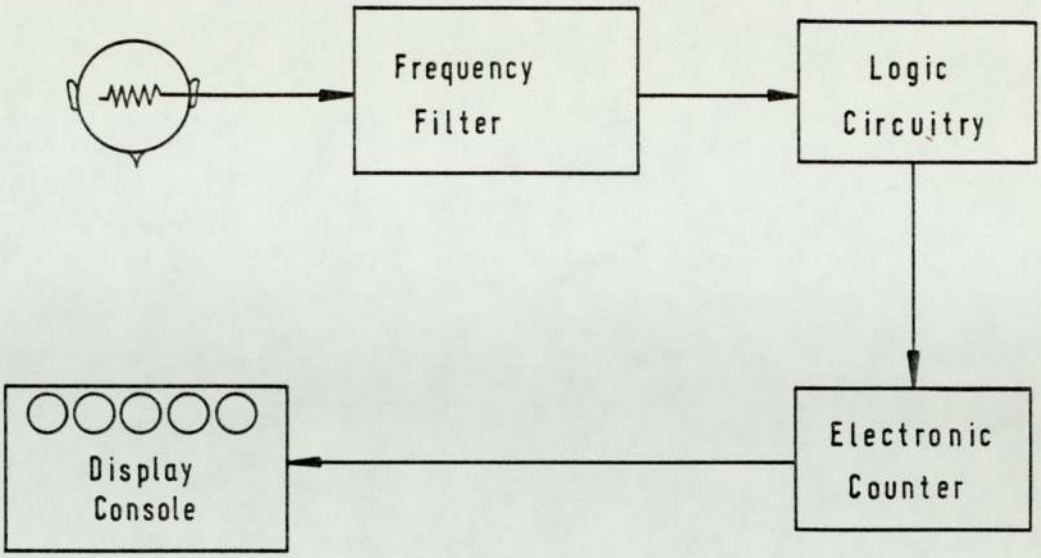


Fig. 3.1. Basic Biofeedback procedure

Refinements to the biofeedback circuitry have been added so that high voltage spikes would not be inadvertently conditioned (Finley, Smith and Etherton 1975) and to reduce the possibility of accidentally reinforcing irrelevant EEG signals (Kaplan 1975). These variations in technique led to discrepancies in the literature as to the success rate of biofeedback. Controversy exists as to what rhythm was actually being reinforced and what was the relationship between SMR and mu activity (9-13 c.p.s.). Filters were criticised as being too strict or too liberal (Kaplan 1975; Finley et al. 1975). Although SMR was defined in the cat as 12-16 c.p.s. activity, studies on humans include biofeedback of 12-14 c.p.s. (Sterman 1973; Sterman et al. 1974; Kaplan 1974, 1975; Seifert and Lubar 1975; Lubar and Bahler 1976), 11-13 c.p.s. (Finley et al. 1975; Rouse, Peterson and Shapiro 1975), and 6-12 c.p.s. depending on dominant rolandic activity.

Although biofeedback training may reduce the incidence of seizures and the amount of spike and wave activity in the EEG (Sterman 1973; Kaplan 1974,1975; Sterman et al. 1974; Wyler et al. 1976), in only a few cases was there definite evidence for increased power spectra of the reinforced EEG signal after training (Finley et al. 1975; Seifert and Lubar 1975). Kaplan (1974, 1975) stated that if clinical change is directly related to the training of physiological variables, there should be an apparent statistical change in that variable and that in her patients the improved clinical condition was caused by inadvertently training them to function at a lower level of arousal. Other attributing factors may have been better documentation of seizures by the patients and also the influence of placebo effects. However, placebo effects occur in the early stages of new or changed treatments and as all biofeedback studies have been conducted between 2 to 10 months on average, with beneficial effects occurring after 2 to 3 months of regular training, the novelty should have worn off (Sterman et al. 1974; Seifert and Lubar, 1975).

Sterman (1973) postulated that biofeedback led to neuronal reorganisation. However, the theory became unfounded when withdrawal of treatment in 3 patients after 6 months caused a return to pre-training levels of seizure activity. He suggested that withdrawal effects were due to neuronal supersensitivity due to reduced activation of the SMR related circuits. Wyler, Lockard, Ward and Finch (1976) believed that the most obvious factor correlating with reduced clinical seizures through operant conditioning was not the production of any specific EEG frequency but

purely a neuronal desynchronisation, preventing recruitment of surrounding neurons leading to propagation of spike and wave. They proposed that a patient should improve through reinforcement of any rhythm involved in alerting. This proposal of EEG normalisation was supported by Kaplan (1975) and Lubar and Bahler (1976).

It seems that the effectiveness of biofeedback is complicated by type of clinical seizure present in the patient, inadequacy in fully identifying the reinforced activity and alterations in the attention and arousal of subjects. There seems a need for more controlled studies and the exploration of brain rhythms in normal subjects. The main reason for developing biofeedback was to treat severe epileptics resistant to drug therapy - about 25% of all epileptic patients (Seifert and Lubar 1975). These patients take various and multiple anticonvulsants and many are known to cause high frequency spindling, particularly barbiturates. One possibility is that the presence of 12-14 c.p.s. rhythm in an epileptic is due to drug artefact (Kaplan 1975). However, authors advocate the development of biofeedback techniques as a means of encouraging patients to manage their own seizures and thus reduce psychological dependencies and increase self-esteem (Seifert and Lubar 1975; Lubar and Bahler 1976).

There appears to be no mention in the literature of results on biofeedback with photosensitive patients. However, Kaplan (1974) recommends using sensory or reflex epileptics. Previously, conditioning methods have proved to be unsuccessful in this type of patient (see Section 3.1.). Even so Jeavons and Harding (1975) found spike and wave

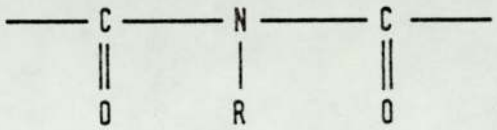
abnormalities in the basic EEG of 54% of photosensitive epileptics. Such patients might prove suitable for biofeedback therapy as regards EEG normalisation. It is foreseeable that problems could arise using visual operant stimuli of the type employed by Sterman (1973). However, as regards photically evoked paroxysms, more control on epileptiform activity would be possible and power spectra might produce more information by EEG sampling preceding the PCR before and after biofeedback.

3.5. Antiepileptic Drugs.

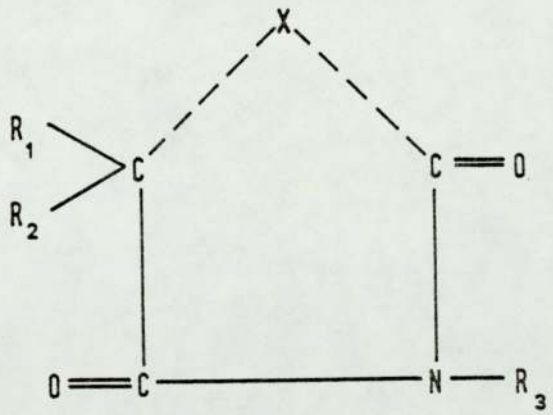
Antiepileptic drugs are often classed as anticonvulsants. However, convulsions are not a necessary manifestation of epilepsy (Meinardi 1971) as a child with simple absence attacks does not convulse as neither do patients with other forms of epilepsy (Grant 1976). Comparisons of antiepileptic drugs requires understanding of their individual pharmacology. Modern day chemotherapy developed from the first effective anticonvulsive medication, Potassium Bromide. This treatment was introduced in the mid-nineteenth century to reduce sexual drive which was then believed to be the root cause of epilepsy (Meinardi 1971; Grant 1976). The control of epilepsy through drug therapy is usually achieved by suppression of excitable neurons, making adjacent normal nerve cells less liable to excitation, or stabilising neuronal membranes by increasing CNS concentrations of inhibitory neurotransmitters or suppressing production of excitatory neurotransmitters (Woodbury and Esplin 1959). Epilepsy is the tendency to recurrent seizures (Jeavons 1972a; Grant 1976). Its diagnosis depends on close study of the clinical history and EEG. Subsequent drug therapy then partly depends on the type of seizures (Jeavons 1975) and treatment should be maintained at full dosage for at least two years after the last seizure has occurred otherwise full-control cannot be affirmed (Jeavons 1972a; Grant 1976). Difficulty in controlling epilepsy occurs in about 20 - 25% of patients (Aird 1970; Jeavons 1972a). It is not uncommon, when a person suffers with two or more types of seizures, for the patient to take several antiepileptic drugs. Multiple drugs can cause

serious intoxication and a possible increase in fit frequency. Withdrawal of drugs is dangerous and needs to be done gradually to avoid status epilepticus (Jeavons 1975) which may cause brain damage or death.

Most of the conventional antiepileptic drugs have an aromatic ring chemical structure. These drugs have a characteristic group of atoms conferring biological activity (a pharmacophore) :-

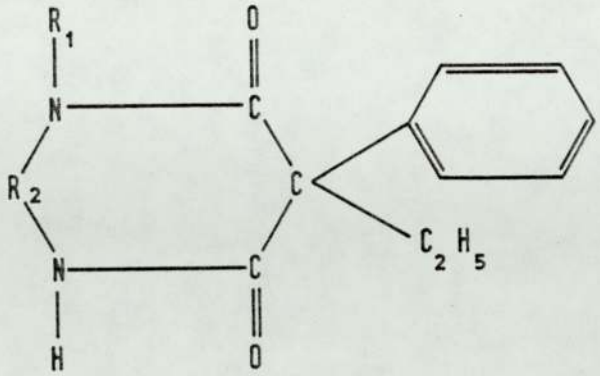


This is usually found in a general structural formula :-



in which R_1, R_2 or R_3 may be a hydrogen atom, - CH_3, C_2H_5, or C_6H_5 radical and where X is another radical characteristic to the group of drugs e.g. -CO-NH-, barbiturates (Reckitt and Coleman 1973).

3.5.1. Barbiturates and Primidone.



	R_1	R_2
Methobarbitone	$-CH_3$	C=O
Phenobarbitone	$-H$	C=O
Primidone (Mysoline)	$-H$	$-C_2H$

Phenobarbitone is one of the oldest, most widely used, least toxic and most effective of all antiepileptic drugs (Glazko 1975). In small doses it is a safe basic drug for adults, many of whom can be kept free from fits on this drug alone (Jeavons 1975). Effective plasma levels are 10 - 20 µg/ml. which can be attained in the daily dose of 1 - 2 mg/kg. of body weight in 2 - 4 weeks (Glazko 1975) but therapeutic serum levels vary widely with different authors (Grant 1976). In children higher dosesof the drug might be required as elimination is greater (Glazko 1975). However, phenobarbitone is not well tolerated in children between 2.5 - 12 years of age (Jeavons 1975) due to irritability,aggression, tearfulness or overactivity, and so should particularly be avoided with brain damaged epileptic children (Grant 1976).

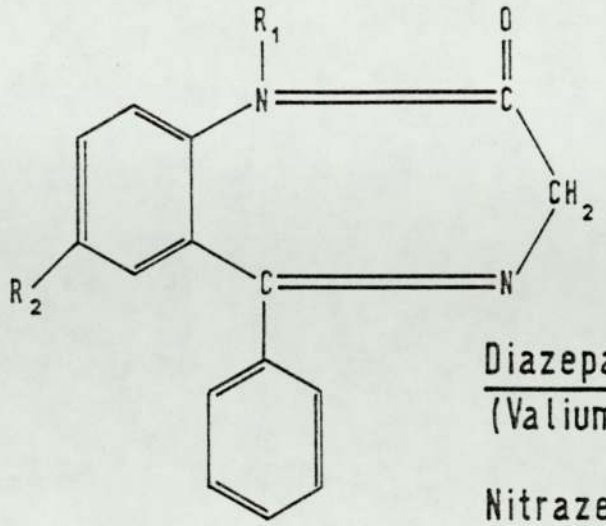
Women tend to require larger doses of phenobarbitone, and primidone (this also applies to phenytoin) per unit

weight than men but blood serum levels remain lower in women (Glazko 1975). Phenobarbitone undergoes slow hydroxylation and like all slow hydroxylators it is prone to toxic effects resulting in sedation, depression and irritability which are often overlooked because of increased tolerance (Jeavons 1975). This drug is efficacious with major motor seizures but also useful for neonatal and febrile convulsion and focal motor or partial seizures (Jeavons 1975; Grant 1976). Phenobarbitone also stimulates the metabolism of many other drugs (Kutt 1975).

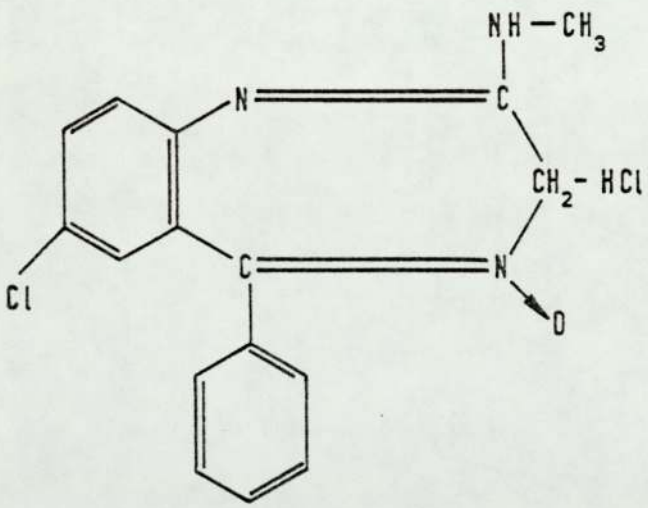
Methobarbitone is less toxic and less potent in the therapy of major seizures.

Primidone (Mysoline) is the 2-desoxy derivative of phenobarbitone and is partly converted to this parent drug in the body (Glazko 1975; Grant 1976). Doses are advised of less than 750 mg/day (Jeavons 1975) as the side effects of primidone are similar to phenobarbitone but more marked (Aird 1970) and in addition can produce vertigo, confusion and skin rashes (Glazko 1975; Grant 1976) even with very small doses in the first week (Jeavons 1975). Primidone is particularly effective against psychomotor epilepsy (Jeavons 1975) and to a lesser extent tonic-clonic seizures and other types of epilepsy except absences (Grant 1976).

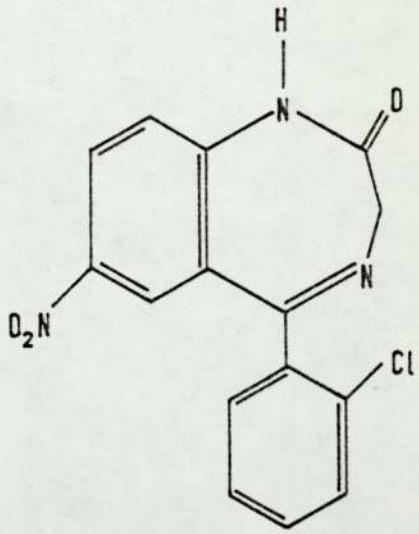
3.5.2. Benzodiazepines.



	R_1	R_2
Diazepam (Valium)	$-CH_3$	$-Cl$
Nitrazepam (Mogadon)	$-H$	$-NO_2$



Chlordiazepoxide (Librium)



Clonazepam (Rivotril)

Benzodiazepines are characterised by a 7-membered heterocyclic ring. They undergo extensive biotransformation in the body (Kutt 1975) but information on plasma levels is meagre. This author also reports that interactions between the benzodiazepines and other drugs is low, the exception being phenytoin which can reach toxic levels through impaired metabolism. All benzodiazepines have tranquillising properties and are therefore useful for patients whose

seizures are aggravated by stress (Jeavons 1975; Grant 1976). These drugs have a profound effect on the EEG resulting in normalisation in cases of generalised or centrencephalic epilepsies (Jeavons 1974). Therefore, when the EEG is being used for diagnostic purposes benzodiazepines should not be given during the two weeks preceding recording. These drugs also produce 20 - 30 c.p.s. low voltage fast activity (LVFA) in the EEG, which first appears in the frontal regions and then spreads posteriorly with a reduction in alpha amplitude (Tower, Beall and King 1962). Increased dosages gradually bring about partial or complete replacement of alpha by LVFA and these effects may persist up to one week after discontinuation of the drugs. These authors also state that in normal subjects, clinical side effects disappear more quickly than the EEG effects.

Chlordiazepoxide (Librium) is useful with generalised epilepsies particularly in children, although benefit occurs in psychiatrically disturbed patients (Jeavons 1975). This drug undergoes N-demethylation to form the major metabolite N-desmethyl chlordiazepoxide which produces lactam demoxepam, found in plasma and urine, as a result of oxidation deamination (Glazko 1975). The further metabolism of demoxepam, which also has anticonvulsant properties, results in some products identical to diazepam metabolism. Glazko (1975), in his summary on chlordiazepoxide research, reports a plasma half-life of 7 - 28 hours with a half-life of demoxepam as 14 - 95 hours.

The potent anticonvulsant action of diazepam (Valium) makes it the major drug in the treatment of status epilepticus by intravenous infusion of 10 - 20 mgm. (Jeavons 1975; Grant 1976). It is probably the most widely used

benzodiazepine. Major metabolic routes again involve N-demethylation and hydroxylation (Glazko 1975) with a gradual decline in plasma levels after termination of the drug, which are still measurable a week later. The most common side effects are ataxia, drowsiness, slow thinking, memory impairment, slurring of speech and apathy (Tower et al. 1962). These side effects can appear five days after commencing the drug and generally disappear three days after discontinuation.

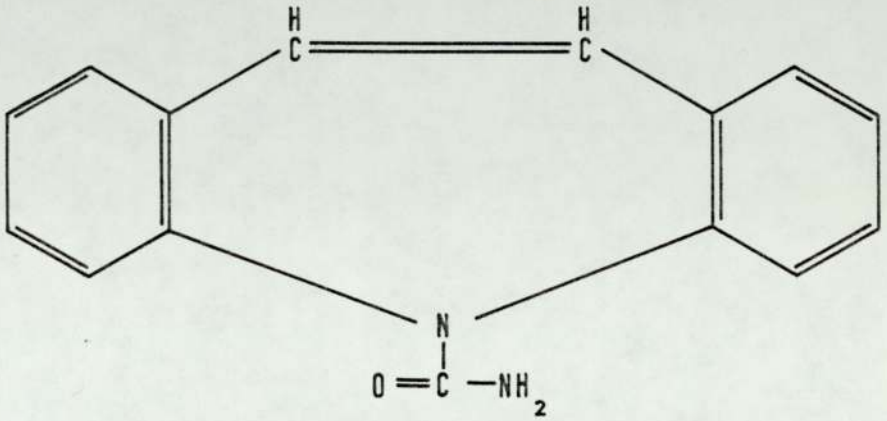
Benzodiazepines are very useful in treating infantile spasms, nitrazem (Mogadon) being particularly effective with this type of seizure and myoclonic astatic petit mal (Jeavons 1975). The 2 c.p.s. spike and wave discharges commonly seen in association with childhood myoclonic epilepsies tend to be inhibited by nitrazepam or clonazepam (Jeavons 1974). Metabolism of nitrazepam involves reduction of the nitro group, in the 7 position of the phenyl ring, by microsomal enzymes to a primary amine which in turn is acetylated to form the major metabolite 7-acetamide nitrazepam (Glazko 1975). Peak plasma levels of nitrazepam occur after about 2 hours with a half-life approximately 25 hours in normal adults through oral dosage (Glazko 1975).

The chemical structure of clonazepam (Rivotril) is identical to nitrazepam except for the o-chlorophenyl ring attached to the C-5 carbon of the diazepine ring (Glazko 1975). Roche describes the pharmodynamics and clinical effects of clonazepam in detail (see Hooshmand and Oliver 1975). Roche Laboratories recommend clonazepam alone or as an adjunctive for the treatment of akinetic, myoclonic and petit mal variant seizures, and in simple absences when ethosuximide has failed.

The maximum dose for adults should not exceed 20 mgm; for children the maximum maintenance dose is less, 0.2 - 0.2 mg/kg/day. Clonazepam is capable of suppressing the spike and wave discharges in absence seizures and diminishing the frequency, amplitude, duration and spread of discharges in minor motor seizures. Single oral dose administration in man produces maximum blood levels of clonazepam within 1 - 2 hours, with a variable half-life of between 18 - 50 hours. The drug undergoes biotransformation into five metabolites through oxidative hydroxylation and amino derivative formation. Adverse reactions of clonazepam involve CNS depression. Studies by Roche show the occurrence of drowsiness in 50% of patients and ataxia in 30% (both of which may diminish in time); behaviour problems in 25%, and a whole range of side effects from skin rashes to respiratory troubles to suicidal attempts in psychiatrically disturbed patients. Also, when the drug is used in patients with several different types of seizures, it may increase the incidence or precipitate the onset of generalised seizures, viz. tonic-clonic fits, necessitating further addition of anticonvulsant therapy. In some studies up to a 30% loss of antiepileptic activity has been reported which in some cases was re-established by dosage adjustment. Overdosage of clonozepam produces somnolence, confusion and even coma. Withdrawal may be dangerous, particularly abrupt discontinuation in long term, high dosage patients. Symptoms include sweating, vomiting, abdominal and muscle cramps, tremors, convulsions and even status epilepticus.

3.5.3. Carbamazepine (Tegretol).

The chemical structure of carbamazepine fits into a dibenzoazepine group and differs from the benzodiazepines in having a 7-membered ring with only one nitrogen atom present. Chemically it is related to imipramine (Glazko 1975; Grant 1976).



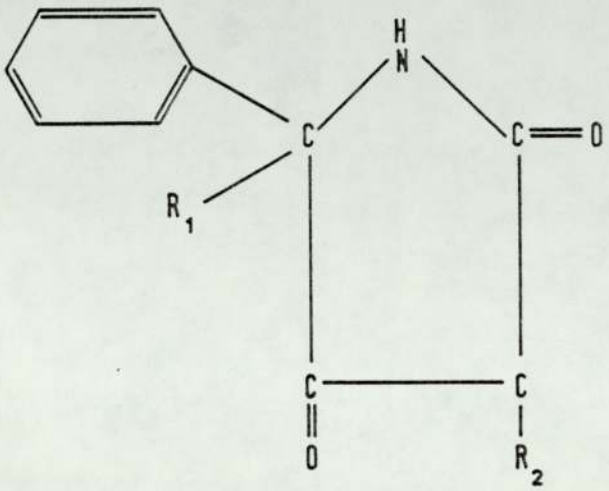
Carbamazepine

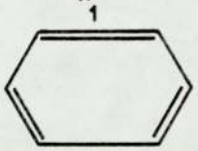
(Tegretol)

Glazko (1975), reporting on the pharmodynamics of carbamazepine, gave peak plasma levels as occurring at 2 - 4 hours in proportion to dosage and reaching plateau levels in about 32 hours. Serum half-life varied between 14 - 36 hours. Carbamazepine is the first drug of choice with psychomotor epilepsy and is also useful for tonic-clonic seizures (Jeavons 1975; Grant 1976). It is a major antiepileptic drug, not merely a supplemental medication, although it does not help all patients and has little influence on absence seizures (Grant 1976). Initial worries about toxicity, in particular bone marrow depression, now seem exaggerated. A psychotropic effect has been noted but not definitely proven (Grant 1976).

Despite the reduction or stoppage of fits, carbamazepine often causes an increase in EEG abnormalities at the same time (Jeavons 1975). However, worsening of the EEG is not an indication for increased dosage.

3.5.4. Hydantoins.



	R_1	R_2
Diphenylhydantoin (Phenytoin, 'Epanutin')		— H
Ethotoin ('Peganone')	— H	— C_2H_5
Methoin ('Mesontoin')	— C_2H_5	— CH_3

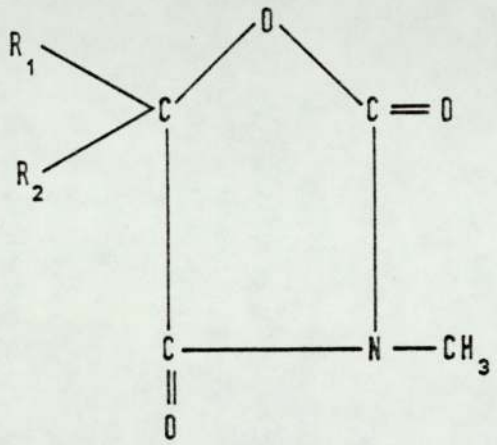
Phenytoin is the most widely studied antiepileptic drug available and is frequently used for many types of epilepsy (Grant 1976). It is very effective with tonic-clonic seizures though often ineffective with focal clonic seizures and absences (which may be exacerbated), (Woodbury and Esplin 1975; Aird 1970; Jeavons 1975; Grant 1976). Standard therapeutic serum levels are 10-20 µg/ml., produced by a dose of 4-5 mg/kg., in adults and with a slightly higher dose in children (Grant 1976). A number

of other antiepileptic drugs cause elevation of phenytoin plasma levels, through inhibition of biotransformation of phenytoin, resulting in a prolonged half-life, e.g. sulthiame, benzodiazepines (Kutt 1975). An individual's response to phenytoin is idiosyncratic but it is uncertain why and probably involves a wide variety of biochemical and genetic factors (Glazko 1975; Kutt 1975). Maximum blood levels of phenytoin occur between 4 - 12 hours after oral administration indicating slow absorption from the intestinal tract (Glazko 1975). This author's research has also shown a half-life ranging from 9 - 42 hours with an oral dose of 0.5 gm. and that phenytoin undergoes slow hydroxylation in the liver. Toxic reactions to phenytoin are fairly frequent and not always dose dependent (Jeavons 1975). Side effects include coarsening of features and the skin, hirsutism, gum hypertrophy, megoblastic anaemia, folic acid deficiency, gastric disturbances and neurotoxicity, viz. fatigue, tremor, nystagmus, ataxia, particularly with overdosage which may lead to cerebellar damage (Aird 1970; Jeavons 1975; Grant 1976). Jeavons (1975) does not advise the use of this drug with females for, besides its adverse effects on appearance, phenytoin has been implicated with teratogenicity in pregnancy more than other anticonvulsants. Due to the idiosyncratic effects of phenytoin small alterations can produce toxic or sub-therapeutic serum levels (Grant 1976). This author has also seen behaviour and personality disturbances in the absence of other clinical signs of phenytoin intoxication which improved with reduced dosage. Research has shown that there is no significant circadian variation in serum phenytoin and no difference in seizure control using

single or divided doses. Grant (1976) therefore recommends giving a single daily dose, preferably in the evening.

The other hydantoinates, ethotoin and methoin, may be effective in patients where phenytoin has failed. Ethotoin is less toxic and less potent; methoin is more toxic than phenytoin (Aird 1970; Grant 1976).

3.5.5. Oxazolidine-diones.



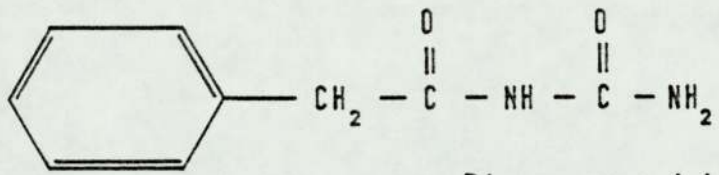
	R_1	R_2
Ethadione	$-C_2H_5$	$-C_2H_5$
Paramethadione ('Paradione')	$-C_2H_5$	$-CH_3$
Trimethadione ('Tridione')	$-CH_3$	$-CH_3$

Glazko (1975) described the chemical structure and metabolism of the oxazolidine-diones. They have a 5-membered ring structure resembling that of the hydantoins except for an oxygen in the one position replacing a nitrogen. The major metabolic pathway involves N-dealkylation with subsequent accumulation of this metabolite in the body and slow elimination.

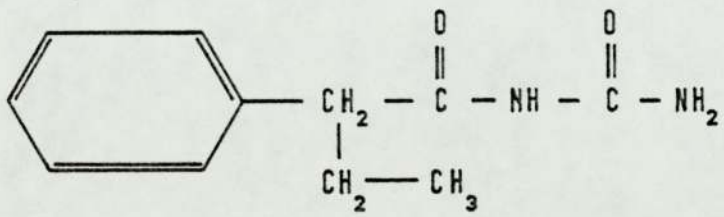
The main metabolite of trimethadione is dimethadione showing somewhat weaker anticonvulsant activity and a longer half-life (about 10 days), so that several weeks are required of daily trimethadione dosage before equilibrium is reached. Dimethadione is an inhibitor of demethylation which may slow down further dealkylation of trimethadione and thus extends its active duration.

Trimethadione and paramethadione are efficacious in controlling absence seizures but have mainly been superseded by ethosuximide due to their greater tendency to produce toxic effects, viz. sedation, skin eruptions, intolerance of bright lights, blood dyscrasias and hepatic or renal damage (Aird 1970; Grant 1976).

3.5.6. Phenylureas.



Phenacemide ('Phenurone')

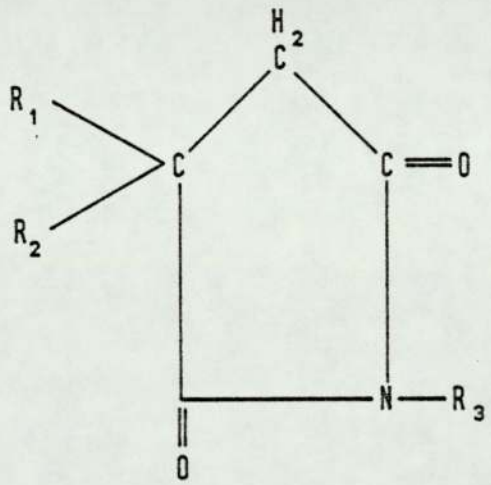


Pheneturide ('Benuride')

The phenylureas are hydantoin derivatives having an open chain structure rather than a closed ring (Glazko 1975). The urea portion of the molecule is split and hydroxylation, with subsequent methylation analgous to phenytoin metabolism, result in catechol metabolites (Glazko 1975).

Their antiepileptic effects may occur in all forms of epilepsy but use is limited by their serious side effects (Aird 1970). Psychomotor epilepsy can be treated with pheneturide (Kutt 1975; Grant 1976). However, to avoid side effects daily doses should not exceed 400 mgm. (Jeavons 1975) and other less toxic and more effective drugs exist (Grant 1976).

3.5.7. Succinimides.



	R_1	R_2	R_3
Ethosuximide ('Zarontin')	C_2H_5	CH_3	H
Methsuximide ('Celontin')		CH_3	CH_3
Phensuximide ('Milontin')		H	CH_3

Ethosuximide undergoes hydroxylation of the ethyl side chain to give two major metabolites (Glazko 1975).

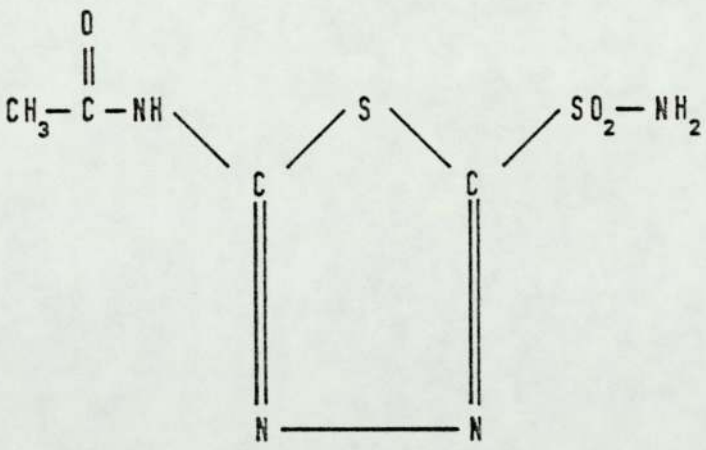
The serum half-life of ethosuximide is about 60 hours in adults and 30 hours in children and is of the same order from administration of single or repeated doses, indicating no significant change in the rate of metabolic disposition. The difference between adults and children is largely unknown but half-lives do not appear to be influenced by the binding of ethosuximide into plasma proteins which is meagre (Glazko 1975). This drug has been the first choice in the treatment of simple absences and is the most effective of the succinimide group (Aird 1970; Grant 1976) effective dosage being around 250 mgm. three times daily. A child with typical absences invariably shows 3 c.p.s. spike and wave in the EEG. Inhibition of these paroxysms may occur with ethosuximide and the drug should only be given when the EEG is characterised by these discharges (Jeavons 1974,1975; Grant 1976). Tonic-clonic seizures may increase in frequency (Grant 1976) and should these occur primidone or phenobarbitone can be added. Combination of either of these two drugs with ethosuximide is also effective for myoclonic jerks (Jeavons 1972a) Side effects normally include gastro-intestinal disorder, drowsiness, leucopenia, agranulocytosis and occasionally headaches, dizziness and psychiatric manifestations (Aird 1970).

The biotransformation of methsuximide involves N-demethylation, hydroxylation and ring cleavage (Glazko 1975). Single dose plasma half-life is approximately 2-3 hours but after repeated doses the half-life decreases, indicating enhanced metabolic disposition. The N-methyl derivative appears to be the dominant metabolite in blood plasm (Glazko 1975). When other drugs have failed in the treatment of psychomotor epilepsy or absences methosuximide may be applic-

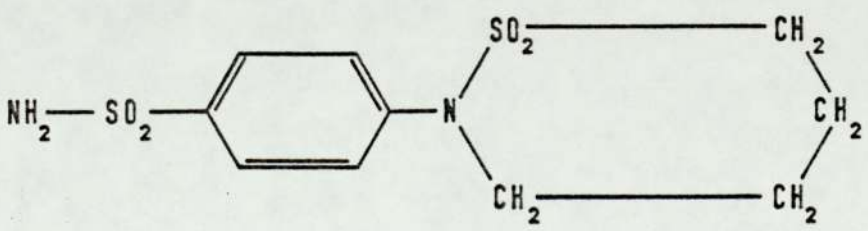
able. It can be used in association with oxazolidinediones or hydantoins in order to enhance their protective effects (Aird 1970). Besides the usual side effects of drowsiness, ataxia, nervousness, double vision, rashes, etc. methsuximide, being slightly more toxic, may cause renal, liver and bone marrow disorders (Aird 1970).

The metabolism of phensuximide is similar to that of methsuximide (Glazko 1975) with plasma half-lives, after single and multiple doses in humans of about 4 hours. The drug is effective in a percentage of cases with typical absences and is the least toxic succinimide (Aird 1970).

3.5.8. Sulfonamides.



Acetazolamide (Diamox)



Sulthiame (Ospolot)

Acetazolamide is a general anticonvulsant having a specific inhibitory effect on the enzyme carbonic anhydrase (Woodbury and Esplin 1959). Rapid absorption occurs through the gastro-intestinal tract producing peak plasma levels 2 - 3 hours after dosing (Glazko 1975). Binding onto plasma protein occurs for 90-95% of the drug and accumulates in body tissues rich in carbonic anhydrase, viz. erythrocytes, renal cortex, stomach, pancreas and brain (Glazko 1975). However, in man most of the drug is excreted unmetabolised within 24 hours. Acetazolamide exerts its antiepileptic effects by altering cell membrane permeability and increasing the ratio of intra- to extra-cellular potassium level in the brain, thus blocking mono-synaptic excitation (Woodbury and Esplin 1959; Aird 1970). It is effective in tonic-clonic seizures and typical absence seizures, originally being suggested for absence seizures (Jeavons 1975). However, benefit can occur in other types of fits, whether generalised or focal. The drug is mainly used as an adjuvant for other anticonvulsants, usually as a single 250 mgm. dose at night (Aird 1970; Jeavons 1975). Variations in fit frequency throughout the menstrual cycle in women can improve with intermittent use of acetazolamide (Aird 1970). The main advantage of this drug is the rarity of side effects as long as the dose does not exceed 500 mgm. daily (Jeavons 1975).

Sulthiame, like acetazolamide, is a carbonic anhydrase inhibitor (Glazko 1975) and reaches peak plasma levels in 1 - 5 hours. It is partly metabolised into a major hydroxylated metabolite. Drug interactions with sulthiame can occur, in particular elevation of phenytoin

levels, thereby prolonging this latter drug's half-life (Glazko 1975; Jeavons 1975; Kutt 1975). Sulthiame is recommended for the use in psychomotor epilepsy but may be effective mainly as a result of the increased phenytoin levels (Jeavons 1975; Grant 1976). Controversy exists as to its benefit in behaviour disturbances (Grant 1976). Sulthiame should not exceed 400 mg/day and toxic effects are frequent, including irritability, paraesthesia, hyperventilation and depression (Jeavons 1975; Grant 1976).

3.6. Antiepileptic Drugs and Photosensitivity.

Many antiepileptic drugs have been developed for the control of specific forms of seizures, the drug of choice depending on the type of fit. However, epileptic attacks may occur spontaneously or be aggravated by certain conditions, viz. stress, where treatment with diazepam could be applicable. Drug control of seizures precipitated by specific stimuli such as flickering light have been of limited success; antiepileptic drugs normally being given to these patients with spontaneous attacks or resting EEG abnormalities (Hess et al. 1974).

A case report on one patient (Marshall and Walker 1951) stated that 'benzedrine' (amphetamine) or phenobarbitone did not affect the photosensitive threshold. A more detailed account by these authors (Marshall et al. 1953) again supported the failure of intravenous phenobarbitone and orally administered amphetamine in this respect. All the patients' attacks had been preceded by exposure to bright and flickering light. Phenytoin, phenobarbitone and bromides had produced some improvement but, as the patient was more vulnerable to attacks when exhausted, tense or nervous, the drugs may have improved these conditions. Bickford et al. (1953) found a suppression of photically induced abnormalities through intravenous injection of trimethadione, sodium amylobarbitone and phenacimide. However, the drugs were given in high doses and produced sedation. Also, long term clinical testing did not parallel the short term effects. When studying the effects of sleep on photically induced seizures, Rodin et al. (1955) found an apparent increase in threshold levels during spontaneous sleep but more so

in drug-induced sleep using sodium amytal, with no evidence that those patients in medicated sleep had reached a deeper level of sleep than spontaneous sleepers. Hutchinson et al. (1958) investigating the case of two female patients who self-induced photosensitive attacks, commented on the unsuccessful clinical effects of trimethadione, chlorpromazine and primidone. In contrast, Andermann et al. (1962) reported diminished sensitivity to low flicker rates but not to high rates when treating self-induced epileptics with antiepileptic medication. Trimethadione and allied compounds were most effective. It should be noted that patients with typical absences were common in this study and trimethadione was previously the drug of choice for this type of seizure. Herrlin (1954), reporting on a large number of epileptic children, found the incidence of normal routine EEGs was relatively higher and that of pathological responses to IPS lower in children with typical absences when treated with trimethadione than in the untreated cases. However, definite conclusions could not be made due to the lack of a similar control group treated with other forms of drugs. In his study, 23% of epileptic children showed a positive response to IPS and of these 56% were on chemotherapy. Pantelakis et al. (1962) reported clinical improvement in 'television-sensitive' patients who were taking phenobarbitone but, whilst on this drug, the patients had also been advised to take precautions while viewing. Bower (1963) again advocated the use of trimethadione and ethosuximide to counteract EEG discharge apparently of sub-cortical origin, but recommended that the routine anticonvulsants, phenytoin or phenobarbitone, should be with-held in the case of television induced seizures,

if only one attack had occurred.

Livingston (1964) and Troupin (1966) state that photo-epileptic seizures are very resistant to anticonvulsants which are of little clinical value. Unsuccessful drug therapy, including trimethadione, has been reported in self-induced seizures (Forster et al. 1965). Two case histories of minor attacks precipitated by bright sunlight were not affected by acetazolamide or phenobarbitone even with the addition of trimethadione or paramethadione, (Brausch and Ferguson 1965). However, in one patient minor seizures were later reduced by ethosuximide.

Poiré, Tassinari, Régis and Gastaut (1967) observed the disappearance of spike and wave activity, provoked by flicker, for up to a few minutes as a result of intravenous valium. Investigating physiological measures in photosensitive patients Ebe, Meier-Ewert and Broughton (1969) noticed abolition of the PMR and suppression of the PCR with intravenous valium. The effects were virtually immediate and seizures were stopped for 2-3 days. The electroretinogram, visual evoked and somatosensory evoked potentials were also modified. Intravenous valium was again employed by Denhoff and Shammas (1968) for increasing the threshold of myoclonic jerking when using the photo-metrazol activation test.

Various combinations of paramethadione, phenytoin, primidone, phenobarbitone or ethosuximide proved ineffective in four cases of pattern-sensitive epilepsy (Chatrian et al. 1970b). Procopis and Jameson (1974) commented that an 18 year old female patient, insensitive to IPS while on phenobarbitone became very sensitive two years later after stopping the drug. Jeavons, Herrick, Maheshwari and Harding (1976) state that there is little evidence of anticonvulsants

affecting the PCR, again the only exception being where IPS induces 3 c.p.s. spike and wave absences (7% in their series) which may respond to ethosuximide. A summary of anti-epileptic drug effects in 44 patients (Jeavons and Harding 1975) indicates that although patients' fits and basic EEG may show improvement, there may be no change in the response to IPS. Phenobarbitone and phenytoin had little effect and ethosuximide was effective in less than half the patients using this drug.

Recent work has highlighted two drugs in the treatment of photosensitivity: clonazepam and sodium valproate (dipropylacetate). Rail (1973) reported that after failure of standard anticonvulsants in controlling self-induced photic seizures, treatment of a few patients with clonazepam (3-6 mg/day) brought complete control with concomitant suppression of IPS provoked abnormalities. However, in two cases, major motor seizures occurred for the first time besides adverse changes in personality. Rail believes that this latter effect was a reaction due to a suppression of the self-inducing act, the completion of which can bring a sense of satisfaction. A report on three photosensitive patients, whose attacks were precipitated by television, sunlight or traffic lights, again remarks on the failure of all standard anticonvulsants including diazepam. Subsequent treatment with clonazepam alone stopped the EEG and clinical signs of photosensitivity even at small doses (1-3 mg/day). Long-term follow-up over 1-4 years with 16-18 mgm. daily dosage removed paroxysmal discharges to IPS, controlled absences and, in two patients, stopped the major motor seizures which had occurred once or twice a year (Hooshmand and Oliver 1975). Ames and Enderstein (1976) reported a

variable outcome of clonazepam therapy (6 mgm. daily) in four photosensitive children suffering from an unusual form of motor epilepsy, often associated with mental retardation. Two patients showed immediate and sustained EEG and clinical improvement. One patient showed immediate but unstable clinical improvement with no EEG improvement. Another patient underwent no EEG or clinical change. Clonazepam has been recommended as the first drug of choice in photosensitive epilepsy (Hooshmand and Oliver 1975). However, clonazepam can produce a variety of adverse reactions in a large proportion of patients (see section 3.5.2), frequently associated with CNS depression. Only a few studies exist on the effect of clonazepam on photosensitivity and, although a small number of patients have received long term therapy, no large trials or controlled trials exist with this drug or indeed with other anticonvulsants, the majority of reports being anecdotal.

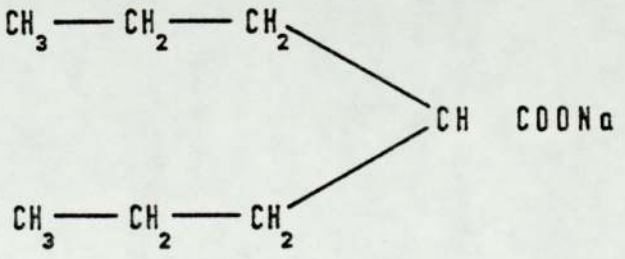
Völzke and Doose (1973) observed a beneficial effect of sodium valproate in removing clinical and EEG manifestations in epilepsy. In one patient with photosensitive epilepsy, seizures disappeared and EEG abnormalities diminished. Sodium valproate has been recommended in the prophylaxis of symptom-free siblings of photosensitive patients showing PCRs on IPS (Doose and Gerken 1973).

4. SODIUM VALPROATE

4.1. Chemical Structure and Synthesis.

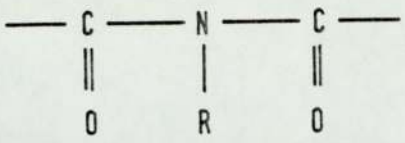
Dipropylacetic acid (DPA) was first synthesised in 1881 but it was not until 1963 that Meunier, Carraz, Meunier, Eymard and Aimard reported anticonvulsant properties of this drug. Meunier and his colleagues, when using DPA as a solvent for khelline derivatives, accidentally discovered that it was the solvent that protected rabbits from cardiazolic induced seizures. Since then, there has been increasing research into the pharmokinetic and pharmodynamic properties of DPA. The generic name for DPA is valproic acid and it is the sodium salt, sodium valproate or sodium di-n-propylacetate, that is the usually available form of the acid although the magnesium salt has occasionally been used (Pinder, Brogden, Speight and Avery 1977). Sodium valproate is a white, odourless crystallire powder which has a saline taste. The molecular weight has been quoted as 144 (Miribel and Marinier 1968; Meijer and Meinardi 1975) and as 166 (Reckitt and Coleman 1973). It is highly soluble in water and alcohol, contains 86.8 of the acid and has a pKa of 4.95 (Swinyard 1964; Meijer and Meinardi 1975).

The chemical structure of sodium valproate is unique amongst anticonvulsants as it does not contain a nitrogen atom in its molecule and it is a fatty acid of linearly symmetric chains (Olive, Tridon, Weber, Vidailhet and Pierson 1969).



Sodium Valproate

The majority of anticonvulsant drugs are heterocyclic and possess the pharmacophore :-



The metabolism of sodium valproate, therefore, differs from that of existing anticonvulsants (Reckitt and Coleman 1973). The trade name for sodium valproate in the UK is Epilim. Overseas this drug may be sold under trade names of Depakine, Dépakene, Urekene, Ergenyl, Labazene (Reckitt and Coleman 1973).

4.2. Pharmodynamics.

Animal studies on newly proposed antiepileptic drugs usually involve batteries of tests, viz. maximal electroshock seizure patterns (MES); minimal electroshock threshold (EST); the subcutaneous metrazol seizure test; and other chemically induced and audiogenic seizure tests. The MES and EST are supposedly useful models for temporal lobe or psychomotor epilepsy in humans. Similarly MES parallels generalised tonic-clonic seizures and audiogenic seizures in mice, and carbon dioxide withdrawal seizures in rats are models of absence seizures in man (Pinder et al. 1977). Non-toxic doses of sodium valproate were found to elevate the threshold for EST and metrazol seizures in mice and rats, abolish audiogenic seizures in mice and prevent carbon dioxide withdrawal seizures in rats (Swinyard 1964). Similar protection was found in cats and rabbits subjected to the MES test. Such animal studies have shown sodium valproate to be less potent than phenobarbitone, diphenylhydantoin and phenecamide, but more potent than trimethadoine (Swinyard 1964; Reckitt and Coleman 1973). However, the protective index for metrazolic seizures (ratio of effective dose ED50 to neurotoxic dose TD50) was significantly higher for sodium valproate than for phenecamide and similar to phenobarbitone and trimethadione. Other authors have reported DPA as efficacious in non-toxic doses up to 200 mg/kg bodyweight in protecting mice, rats and rabbits against audiogenic, electrically and chemically induced seizures (viz. cardiazol or pentetrazol convulsions), (De Biolley and Sorel 1969a; Carraz, Boucherlé, Lebreton, Benoit-Guyod and Boitard 1964a; Dumon-Radermecker 1969; Lebreton, Carraz, Meunier and Beriel 1964b). However, DPA does not afford protection against

convulsions induced by pictrotoxin, strychnine, thuyones and cocaine (Lebreton et al. 1964b; Olive et al. 1969; Reckitt and Coleman 1973). Various amide derivatives of DPA have also been shown to have anticonvulsant, sedative or convulsant properties (Carraz 1968), and one of these compounds, dipropylacetamide, has been found to restrain pictrotoxin, thuyone and strychnine induced seizures.

Cobalt or aluminal brain lesions in animals are the experimental models of focal seizures with elementary symptomatology and chronic epilepsy when situated in the hippocampus (Reckitt and Coleman 1973; Pinder et al. 1977). Cobalt does not produce discrete lesions but leads to biochemical modifications in cerebral metabolism. The resultant motor manifestations and EEG changes of this epileptic model respond to sodium valproate (Reckitt and Coleman 1973). This drug does not reduce the focal discharges in cortical lesions which have been produced by the injection of alumina gel creating a permanent epileptic focus. However, sodium valproate exerts an inhibiting effect on the spread of seizure activity from such epileptic foci (Reckitt and Coleman 1973; van Duijn and Beckman 1975; Pinder et al. 1977). In the focal epileptic model, sodium valproate is comparable to the effect of phenobarbitone but is less effective than diazepam in suppressing inter-ictal phenomena (van Duijn and Beckman 1975).

4.2.1. Toxicology.

Swinyard (1964) determining the LD50 of sodium valproate (the dose of the respective drug which is fatal to 50% of animals within 24 hours) and TD50 (the dose which produces minimal evidence of neurotoxicity in 50% of animals at

the time of peak drug effect) discovered that sodium valproate has a toxicity ranking intermediate to that of clinically used antiepileptic drugs. Its LD50 and TD50 were smaller than those of phenacimide or trimethadione but larger than diphenylhydantoin and phenobarbitol. Generally, acute toxicity of sodium valproate in animals is low and ranges from 565 mg/kg.(ip) in cats to 1700 mg/kg.(po) in mice (Reckitt and Coleman 1973; Pinder et al. 1977). In a variety of species, studies on long-term chronic toxicity over 100-160 days showed no toxic signs even at very high doses (Reckitt and Coleman 1973). The toxicity in rats at the usual doses was negligible (Dumon-Radermecker 1969). De Biolley and Sorel (1969a) found that doses of 400-800 mg/kg. daily of DPA in rabbits produced no toxic signs, but similar doses in mice (400 mg/kg/day) caused a significantly higher incidence of deaths than in control animals. It appears that the LD50 increases with increase in animal size. Long term chronic toxicity up to a year showed no macro- nor microscopic lesions, no abnormalities in the histology of organs, nor changes in the haemograms of sacrificed animals or fatalities (Olive et al. 1969; Reckitt and Coleman 1973). In man, no real toxic effects were observed with a dose of 1200 mgm. of sodium valproate daily (Mairlot 1970). A suicide attempt and a few accidental overdosages of 30-36gm. have resulted in uneventful recovery, (Reckitt and Coleman 1973; Pinder at al. 1977).

4.3. Pharmokinetics.

4.3.1. Absorption, elimination and excretion.

On an empty stomach, sodium valproate is rapidly absorbed as the free acid. This absorption is delayed after a meal (Meijer and Meinardi 1975). Assessment of blood levels of sodium valproate is difficult due to the short half-life of the drug which is of the same order in adults and children (Barnes and Bower 1975). Half-lives have been determined in epileptics as between 8-15 hours (Meijer and Meinardi 1975); 5.6 - 9.6 hours with a mean of 7.4 hours (Espir, Benton, Will, Hayes and Walker 1975); 3.84 - 8.28 hours, mean 5.88 hours (Richens, Scoular, Ahmad and Jordan 1975). Most half-life determinations have been made on chronic epileptic patients where sodium valproate has been added to the existing antiepileptic therapy. In such cases the serum half-life may be shorter but in cases of overdosage longer (Pinder et al. 1977). A study in normal volunteers given a single dose of 600 mgm. after an overnight fast, produced longer serum half-lives of 6.67 - 15.77 hours, mean 9 hours, than in epileptics given a single dose of 800 mgm. (Richens et al. 1975). These and other authors have found that the half-life of sodium valproate is shorter than that of phenobarbitone, diphenylhydantoin or phenytoin (Espir et al. 1975; Meijer and Meinardi 1975; Price 1975). Also sodium valproate underwent extensive distribution reaching peak blood levels within 0.5 - 2 hours.

Animal studies have shown that sodium valproate is mainly excreted by the kidneys and that the liver plays no important role in its metabolic degradation and excretion. Bilateral nephrectomy prolonged the anticonvulsant action of sodium valproate but this was totally unaffected by liver

damage induced by carbon tetrachloride (Swinyard 1964). Administration of the 14C-labelled drug (iv) in mice produced radioactivity in the urine and bile within 15 minutes (Schobben and van der Kleijn 1974). Metabolism of sodium valproate in man is probably as rapid as in animals with small renal excretion of the unchanged drug (Schobben, van der Kleijn and Gabreels 1975). About one-third of the drug escapes degradation and is eliminated as a glucouronide conjugate and other products of omega side chain oxidation by kidney metabolism (Meijer and Meinardi 1975; Pinder et al. 1977). Jordan, Shillingford and Steed (1975) found that in the urine excreted products of sodium valproate 60% was excreted in the unaltered form, i.e. both 'free' and conjugated, of which 10% constituted the free form. Labelling the carboxyl group of DPA with 14C led to the recovery of 13-18% of the radioactivity in respired carbon dioxide in rats, suggesting the drug also undergoes beta oxidation, (Meijer and Meinardi 1975). Elimination is therefore mainly in the urine with small amounts in the faeces and expired air (Pinder et al. 1977).

As serum half-life varies so does the rate of clearance, ranging between 3.5 - 14.4 ml/kg/hr (Espir et al. 1975). However, the rate of plasma clearance is generally high in epileptics and this has been attributed to the increased distribution volume in these patients and also to the probable drug-induced acceleration of adjunctive sodium valproate by existing medication (Richens et al. 1975).

4.3.2. Plasma serum levels.

Sodium valproate is rapidly distributed and reaches the brain of animals within a few minutes. The drug is extensively attached to the plasma proteins (90%) and is mainly restricted to the extra-cellular water in the blood circulation, (Meijer and Meinardi 1975; Pinder et al. 1977). Binding of sodium valproate is also found on human serum albumin (HSA) and although, as the concentration of sodium valproate increases, the percentage binding onto proteins decreases, the most striking difference is seen between the percentage binding to HSA (ca. 60%) and to plasmal protein (ca.90%), (Jordan et al. 1975). These authors also found that binding to alpha and gamma globulin proteins was negligible and that an association appeared to exist between fatty acid levels and the HSA binding, as HSA bound to sodium valproate to a level of 92% at drug serum levels of 50 µg/ml. Ultra-filtrate analysis has shown that sodium valproate can be present in the serum as 5-15%, mean 10%, in the 'free' and unbound form (Espir et al. 1975).

A method for determining the plasma serum levels of sodium valproate was reported by Chard (1975). In a group of out-patients, serum levels were found to vary between 320-637 µmol/l; those with the highest levels showing the greatest improvement, whilst on the drug. Serum levels of patients totally cured whilst on sodium valproate were between 80-240 µg/ml.(Espir et al. 1975). In the same study, patients showing a 50% improvement in fit frequency had serum levels of 60-100 µg/ml. Of other patients who failed to improve even on a 3-4 g/day, 26% had levels of 80 plus µg/ml. All measurements were taken 2 hours after the last dose. It was also evident that

when these epileptics became out-patients, comparison of their drug decay curves during hospital admission showed out-patient serum levels to be generally lower. Despite the short half-life of sodium valproate, Price (1975) found fairly constant plasma levels of the drug measured throughout the day at hourly intervals, even when administered in 3 divided doses. Serum levels ranged between 100-300 plus µg/ml. An approximate correlation between serum levels and dose of 400-2400 mg/day was found when levels were taken 1-3 hours after the mid-day dose in a group of intractable epileptic patients (Hassan, Laljee and Parsonage 1975). A relationship between dose and plasma levels was apparent in another study of chronic epileptics when sodium valproate was added to existing anti-epileptic therapy. Measurements at regular intervals gave a therapeutic range between 50-100 µg/ml. However, individual differences were wide. Single dose administration of 800 mgm. of sodium valproate in long-stay patients produced peak plasma levels of 59.7 - 92.5 µg/ml, mean 70.7 µg/ml., and similarly 600 mgm. given to normal controls gave variable readings of 40 - 90 µg/ml, mean 54.46 µg/ml. (Richens et al. 1975). The same study involved a double blind crossover in patients with 1200 mg/day and placebo tablets. Plasma levels in four patients measured 5-6 hours after the lunchtime dose ranged from 237 - 475 µmol/l, i.e. 34-68 µg/ml.

A good correlation has not yet been determined between daily dose, plasma levels and therapeutic variations mainly due to individual differences and also to the great variation amongst researchers in the chosen dose and the time interval between that dose and blood sampling. Also, most patients were receiving other antiepileptic medication

in addition to sodium valproate. However, therapeutic blood levels appear to be in the region of 50 - 100 µg/ml. as most patients with blood levels within this range appear adequately controlled (Pinder et al. 1977). Levels of 200 µg/ml. should only be exceeded with caution (Reckitt and Coleman 1973).

4.4. Delayed Release Forms.

Due to the interdose fluctuations in plasma levels of sodium valproate certain slow-release derivatives of DPA have been investigated. Meijer and Meinardi (1975) tested several chemical modifications of DPA in order to alter the rate of absorption and elimination in the body. In animals, 2,2 dipropyl-ethanol and 2,3 dipropyl-ethyl esters proved too toxic. However, glycerol tri-dipropylacetate had all the properties of a slow-release preparation and was employable. Another derivative, depamide, has a half-life of up to 15 hours, almost double that of sodium valproate, but is not as efficient as slow release formulations or enteric-coated DPA in smoothing out blood level fluctuations during the day (Pinder et al. 1977). As sodium valproate forms the free acid in the stomach (Meijer and Meinardi 1975), which can be an irritant to the intestinal lining if the tablets are taken on an empty stomach, the enteric-coated tablets would have the advantage of greatly reducing this most frequent side effect (see Section 4.12.5).

4.5. Dosage.

Sodium valproate is available as scored white tablets (200 mgm) or as a cherry-red flavoured syrup (200 mgm/ 5 ml) (Reckitt and Coleman 1973). Authors' recommended daily dosages tend to vary due to the severity of epilepsy in their patients and the extent to which patients have remained on existing medication. Optimum dosage has been quoted anywhere between 600 - 1500 mg/day for the 15-25+ age group, depending on whether the drug was used alone or as an adjunctive with other medication (Fau and Garrel 1968; De Biolley and Sorel 1969a; Dumon-Radermecker 1969; Olive et al. 1969; Espir et al. 1975). Harwood and Harwood (1975) administered sodium valproate in dosages as small as 600 mg/ day to as large as 3200 mgm. daily.

In children dosage should be given in relation to weight and not age (Reckitt and Coleman 1973). Therapeutic trials with children have adopted dosages of 20-30 mg/kg. (Fau and Garrel 1968); 100-800 mgm, daily up to the age of 15 years (De Biolley and Sorel 1969a); an average of 20 mg/kg/ day (Dumon-Radermecker 1969); principally 40 mg/kg/day (Olive et al. 1969); 20-80 mg/kg daily (Barnes and Bower 1975); a mean dosage of 48 mg/kg/day (Grant and Barot 1975).

The majority of authors have found that progressively reducing and in some cases eventually stopping previous anticonvulsants, particularly barbiturates and the least effective drugs of multiple medication, generally benefited the patient, (Duman-Radermecker 1969; Olive et al. 1969; Barnes and Bower 1975; Grant and Barot 1975). The phasing out of existing drugs when introducing sodium valproate should be gradual, particularly with intractable epileptics, to minimise any risk of status epilepticus. Authors vary as to

the initial dose of sodium valproate when commencing treatment. Preliminary dosage of 400 mg/day in divided doses was used by Grant and Barot (1975) and Hassan et al. (1975); 400 and 200 mg/kg/day being added 4 and 3 days later respectively with gradual increase thereafter until maintenance level was reached. Initial dosages of 600 mgm. daily in divided doses are permissible (Reckitt and Coleman 1973; Espir et al. 1975).

The minimum reported maintenance dose is 150 mgm. of sodium valproate daily, which proved sufficient to control typical absence seizures in one child when the drug was added to existing medication (Heathfield, Dunlop, Karanjia and Retsas 1975). The maximum daily dose used to achieve complete control appears to be 5 gm. (Price 1975). In general the most effective dose range in adults is within 1000-1600 mgm. daily with a maximum of 2600 mg/day. For children maintenance levels are usually between 20-30 mg/kg/day and up to 50 mg/kg/day in severe cases (Reckitt and Coleman 1973). Barnes and Bower (1975) found that in children daily dosages above this were unlikely to add further benefit in seizure control.

Eight children became fully controlled of absence seizures on 1000 - 1400 mgm. daily, which was equivalent to 25 - 50 mg/kg/day (mean 36 mg/kg). Their serum levels, taken 1.5 - 3 hours after the last dose, ranged from 42 - 148 µg/ml. with an average of 110 µg/ml. (Haigh and Forsyth 1975). Due to wide variation between patients, these authors were unable to suggest a dose which would achieve a serum level within the therapeutic range of 60 - 100 µg/ml. In agreement are Hassan et al. (1975) who reported that no statistical significance existed between the clinical response to treatment,

the duration of the epileptic history, the duration of treatment or the dosages of sodium valproate. Grant and Barot (1975) also found no correlation between dosage and percentage reduction in seizure frequency. However, Vajda, Morris, Drummer and Bladin (1975) measuring plasma levels at 'regular intervals' found that for individual patients serum levels rose in a linear fashion with increased dosage of sodium valproate and, although individual differences were marked, both variables showed a satisfactory relationship within the individual, with stable plasma levels on a fixed dose.

The standard regime of three divided doses each day at meal times may result in large fluctuations in serum levels due to the short half-life of DPA (Meijer and Meinardi, 1975). Despite this, frequent administration may not be necessary and for chronic epileptics a 500 mgm. tablet would be useful (Price 1975). In children it may be more convenient to give the drug twice a day in order to avoid the problem of a mid-day dose at school.

In conclusion, it appears that serum levels may well be an unreliable measure of the efficacy of sodium valproate. The relationship between serum levels and the the effect on the brain is largely unknown and a therapeutic effect may be operating at low serum levels (Richens et al. 1975). Monitoring a series of fasting blood levels may enable close optimisation (Pinder et al. 1977) and is definitely advisable if the dosage exceeds 50 mg/kg daily.

4.6. Distribution.

The administration of ^{14}C labelled sodium valproate in rodents has shown that the drug is rapidly distributed and reaches grey matter structures within a few minutes of intravenous injection (Schobben and van der Kleijn 1974). However, levels were always three times higher in the liver and kidneys than in the brain. In mouse brain it was evident that sodium valproate was initially homogeneously distributed except for the cerebellum where the white matter showed more activity than in the cortex. It is apparent that the drug becomes principally localised in the caudate nucleus and putamen, nucleus accumbens, midbrain reticular formation, substantia nigra and red nucleus (Ciesieleski, Maitre, Cash and Mandel 1975); these being areas of highest levels of gamma-aminobutyric acid (GABA) degradative enzyme — gamma-aminobutyric acid transaminase (GABAT). Many antiepileptic drugs accumulate in the yellow ligaments of the brain, a feature which is seen with sodium valproate in rhesus monkeys (Schobben, van der Kleijn, Vree and Guelen 1977).

In humans the volume of distribution for sodium valproate is small compared to other anticonvulsants. It has been measured as 0.2 l/kg (Meijer and Meinardi 1975), and 0.15 - 0.40 l/kg. (Schobben et al. 1975), which correlates well with those in animals (Schobben and van der Kleijn 1974). The opinion of these authors is that the distribution of sodium valproate is mainly restricted to the quickly exchanging extracellular water and, as brain levels of the drug are low, relatively high plasma levels will be needed to maintain therapeutic effects.

4.7. Mode of Anticonvulsant Action.

Administration of 200 or 400 mg/kg (ip) of DPA in rats resulted in increased levels of brain GABA by 30-46% after one hour, whereas other amino acids were unaffected (Godin, Heiner, Mark and Mandel 1969). Biosynthesis from glutamic acid was also unchanged and it was proposed that the alteration in GABA level was probably the result of a reduction in its catabolism. The study showed that in vitro DPA inhibited the synthetic enzyme, glutamate decarboxylate (GAD) but, in particular, inhibition was more pronounced on the degradative enzyme, GABAT. In vivo no alteration occurred in either GAD or GABAT activities, but this lack of effect may have been due to the use of a highly diluted drug solution. A similar study showed that DPA protected all mice against the MES test 30 minutes after treatment. Maximal anticonvulsant activity coincided with changes in GABA and cyclic guanosine monophosphate (cGMP). Cerebellar GABA was increased by 62% and cGMP reduced to 39% of the levels in control animals. Cyclic adenine monophosphate (cAMP) was unaffected (Lust, Kupferberg, Passonneau and Penry 1975). In this study, injection of the convulsant isoniazid (200 mg/kg. ip) increased cerebellar cGMP to 337% and reduced GABA to 73% of control levels after 30 minutes. When DPA was given in conjunction with isoniazid, the former offset the action of the convulsant during the 30 minutes. Thereafter the effect of isoniazid predominated for up to 4 hours. It was concluded that DPA exerted a similar effect on the levels of GABA in both the cortex and the cerebellum and, although the changes were not large, GABA concentration was greater in the cerebellum.

The mammalian cerebellum resembles the cerebrum in possessing a cortical rind of grey matter covering a more central mass of white matter and island nuclei (Smith 1970). Cerebellar function is to generally co-ordinate muscular movements. The output signals from the cerebellar cortex are carried on the axons of Purkinje cells (P-cells) which are inhibitory in nature. Several investigators have shown that some antiepileptic drugs increase the output from P-cells e.g. phenytoin, phenobarbitone and diazepam by reducing the cerebellar concentration of cGMP. The net effect is enhancement of the inhibitory output (Lust et al. 1975). This study shows that sodium valproate may be unique among the class of antiepileptic drugs in that it both raises the GABA levels and and lowers the cGMP levels in the brain. However, according to Pinder et al. (1977) these effects occur in animals at dose levels which are unlikely to be achieved during the treatment of epileptic patients. Also, despite the correlation between the anticonvulsive effects of sodium valproate, for several types of seizures in animals with elevation of the whole brain and cerebellar GABA, distinction has not been made between the GABA pool involved in neurotransmission and the larger one association with metabolism in the krebs cycle.

Harvey (1975) discusses the evidence that sodium valproate exerts an antiepileptic action through its effect on brain GABA :-

(i) The protection from audiogenic seizures in mice shows that a direct relationship exists between increase in GABA with increase in sodium valproate dose.

(ii) Seizure activity in ethanol-dependent mice, when

removed from an ethanolic atmosphere, corresponds to a drop in total brain GABA as well as alterations in brain stem level of catecholamines. Treatment with sodium valproate protects against seizures and sustains total brain GABA levels in these mice.

(iii) Sodium valproate does not inhibit GABAT at concentrations of 5 and 10 mM but it does inhibit succinic semialdehyde dehydrogenase (SSAD) which converts succinic semialdehyde to succinic acid in the krebs cycle. However, dose levels required to significantly inhibit the degradative enzyme (i.e. more than 50% inhibition to produce a significant elevation in GABA levels) is much greater than the dose levels which do protect animals against experimentally-induced seizures. Also, in vitro, moderate concentrations of sodium valproate do not inhibit GABAT significantly but do inhibit SSAD. In vivo, experiments on rats, given 400 - 600 mg/kg. of the drug, show a significant rise in GABA levels which is correlated with inhibition of seizure activity and apparent inhibition of GABAT. There is no correlation between seizure activity and inhibition of SSAD (Harvey 1975).

These observations on the enzyme GABAT are contrary to the findings of Godin and his colleagues described above. Obviously there is no straightforward explanation for the anticonvulsant action of sodium valproate being mediated solely by elevation of brain GABA by enzyme inhibition (Harvey 1975).

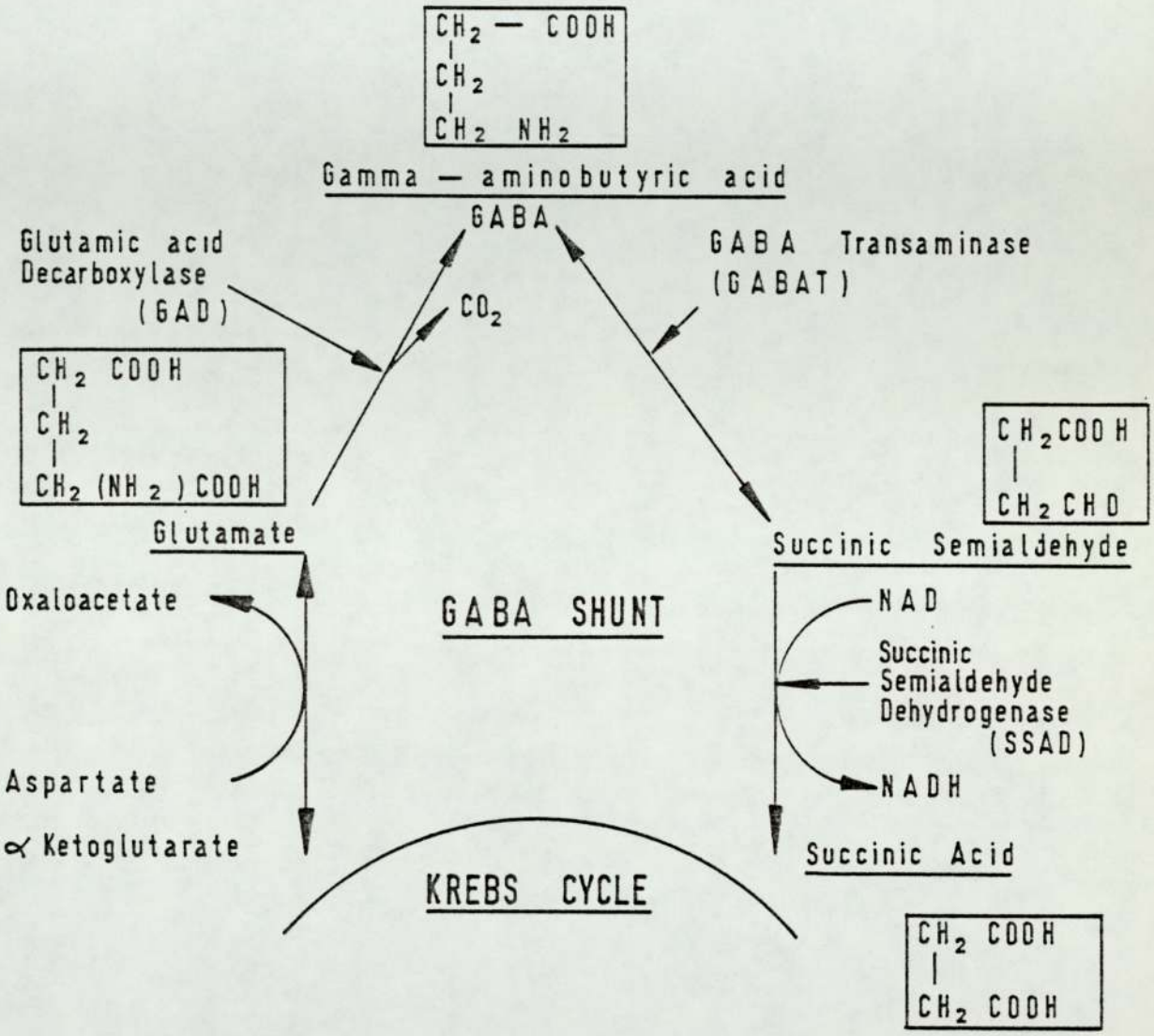


Fig. 4.1. GABA Metabolism in Man

(iv) There is indication from France that sodium valproate blocks the re-uptake of GABA into cerebral cortical slices. As yet there are no reports on the effect of iontophoretic application of the drug to neuronal membranes which may show a completely different mode of action by direct effect of sodium valproate on the cell membrane (Harvey (1975).

Further doubts that DPA exerts its anticonvulsant effect solely by elevating GABA levels was provided by Voskuyl, Ter keurs and Meinardi (1975). When penicillin was added in vitro to guinea pig cortex, increased firing occurred in the number of positive spikes. This penicillin effect is suppressed by the addition of sodium valproate to the fluid but not by adding GABA. However, GABA and sodium valproate both exert similar depressant action on the cortical slice in the absence of penicillin.

All agents which elevate brain GABA also possess anticonvulsant activity, although there is no simple relationship between convulsive activity and GABA levels (Godin et al. 1969). As regards sodium valproate, controversy exists as to the relationship between GABA levels and brain excitation. It is possible that the choice of brain region analysed may in part account for the disparity (Lust et al. 1975). Insignificant changes in GABA levels associated with definite anticonvulsive action of sodium valproate indicate the involvement of other factors (Pinder et al. 1977). Huntingdon's chorea is characterised by reduced levels of brain GABA. A double blind crossover study using 1500 mgm. daily of sodium valproate above and in conjunction

with GABA (24.5 g/day) in eight patients with Huntingdon's chorea, proved that neither treatment was effective in relieving the motor signs of the disease but the combined treatment did increase the central turnover of dopamine and serotonin (Shoulson, Kartzinel and Chase 1976). Dopamine is metabolised to nor-adrenalin from which further metabolism involves two degradative enzymes, one of which is monoamine oxidase (MAO) (Smith 1970). Serotonin or 5-hydroxytryptamine (5-HT) can have the same type of physiological effect as adrenalin although it is less powerful. Sodium valproate has also been shown to potentiate the effects of MAO inhibitors and thymoleptics (Pinder et al. 1977).

4.8. Interaction with other Drugs.

When Meunier et al. (1963) first reported the anticonvulsive action of DPA, they noted the potentialising effect on barbiturates. This was later confirmed by Carraz, Beriel, Luu-Duc and Lebreton (1965). DPA was also found to enhance the hypnotic effect of chloral. Decreasing the dose of DPA given to mice (ip) proportionately reduced the duration of sleep (Lebreton et al. 1964a). Similarly these authors showed that DPA had a potentialising action on the hypnotic effect of mebubarbital and hexobarbital, and slightly induced the hypnotic effect of hemineurine and phenobarbitol. De Biolley and Sorel (1969a) found that with combined medication it was unnecessary to surpass the dose of 200 mgm. of barbiturates or 1-2 tablets of mysoline when using an average daily dose of 600 - 800 mgm. of sodium valproate. Sleepiness was remedied by reducing the dose of other anticonvulsants, principally mysoline and the barbiturates. Sodium valproate may aggravate the side effects of other drugs. Haigh and Forsyth (1975) report drowsiness when sodium valproate was added to a bromide mix or primidone, and ataxia when used in conjunction with phenytoin. All these reactions disappeared with a reduction in original medication. These effects were noted by Noronha and Bevan (1975). and were attributed to raised serum levels of other anticonvulsants by sodium valproate. Of 94 patients with chronic partial or focal epilepsy, one third had a significant rise in phenobarbitone levels (i.e. an increase of 30% plus over the initial value) when sodium valproate was used in conjunction with other antiepileptic drugs (Harwood and Harvey 1975). However, in nearly all instances drowsiness dis-

appeared, with reduction in primidone or phenobarbitone. It was also possible to withdraw carbamazepine, pheneturide and nitrazepam in some cases. A double blind crossover study in 8 normal volunteers involved EEG ratings for the amount of drowsiness and sleep 1-1½ hours after taking 400 mgm. of sodium valproate, 60 mgm. of phenobarbitone, both drugs together, and a placebo. Visual analysis of the sleep stages showed a significant hypnotic effect with sodium valproate, which was enhanced when taken together with phenobarbitone (Scott, Boxer, and Herzberg 1975). Unfortunately the variable, duration of sleep, was omitted from this study. Also graphed sleep stages for each treatment show than in fact the placebo had a more 'hypnotic' effect on the patients than phenobarbitone per se. Barbiturates produce fast activity in the EEG and sodium valproate also appears to influence background rhythms which may present problems when visually interpreting sleep stages.

Most studies with sodium valproate have been open and uncontrolled and testing the effectiveness of the drug has mainly involved adding it to existing anticonvulsants with some adjustment in their dosages. An adjunction of an inefficient dose of DPA to an inefficient dose of phenobarbitol produced a mixture of complete anticonvulsive action in protecting animals from cardiazolic seizures (Lebreton et al. 1964b). Of 90 intractable epileptics, 75 were being treated with 2-4 other antiepileptic drugs, 10 were taking one other drug and 5 had not received any chemotherapy. Existing anticonvulsants included phenytoin, phenobarbitone, ethosuximide, sulthiame, carbamazepine, diazepam and nitrazepam. Dosage of sodium valproate was between 400-2400 mg/day and in

several cases complete control occurred with low level doses (Hassan et al. 1975). Despite reports of its anti-convulsive activity in animals, it has been suggested that sodium valproate has no antiepileptic action per se but acts by raising blood levels of other anti-epileptic drugs (Pinder et al. 1977).

The belief is that sodium valproate probably competes for binding sites with other anticonvulsants on plasma proteins. When given together sodium valproate caused a rise in blood levels of phenobarbitone. In 6 epileptic patients a percentage increase in phenobarbitone was found to be 34-71%, with a significant average increase of 46% (Vakil, Critchley, Philips, Fahim, Haydock, Cocks and Dyer 1975). These authors also investigated a group of patients taking phenytoin and sodium valproate. No significant difference was found in phenytoin levels until the addition of sodium valproate. The initial dose of 600 mg/day caused phenytoin levels to fall but when sodium valproate dosage rose to 1-1.6 gm., phenytoin levels returned to normal. Richens et al. (1975) in a double blind crossover study on 20 long-stay epileptics treated with 1200 mgm. daily or placebo with the established medication found, in agreement with Vakil et al. (1975), a consistent rise of 17-48% in phenobarbitone levels, mean 27%, but serum phenytoin levels showed no significant changes. However Vajda et al. (1975) found 3 cases of phenytoin toxicity when sodium valproate was added to the unchanged dose of phenytoin in 5 severely epileptic patients. Toxicity occurred at high doses of sodium valproate (up to 2 grams) and was associated with a rise in plasma phenytoin levels with concomitant EEG changes.

Reducing the dose of sodium valproate resulted in a fall of this drug's serum levels and those of phenytoin. A dose of 20 mg/kg/day of sodium valproate caused a fall in plasma phenytoin levels in 3 patients (Penry, Porter, Sato, Reddenbough and Dreifuss 1975). Even with constant dosage of phenytoin and ethosuximide, stable serum levels of these drugs were not maintained. Although ethosuximide levels were reasonably constant, a precipitous decline of up to 50% in serum phenytoin occurred at the onset of DPA therapy within 48 hours. The withdrawal of phenytoin in one child, also taking sodium valproate, caused a fall in seizure frequency of over 90% (Barnes and Bower 1975).

The effect of sodium valproate on phenytoin is equivocal compared to the more obvious effects when sodium valproate is combined with phenobarbitone (Pinder, Brogden, Speight and Avery, 1977). Experiments with rats have shown that sodium valproate raises brain phenytoin levels probably through the former drug displacing phenytoin from its protein bound state (Lascelles, in Vakil et al. 1975). Other short chain fatty acids possess similar action so that toxic effects of combined therapy may be due to high concentration of phenytoin in the brain even when plasma levels are low. Authors tend to be uncertain as to whether these drug interactions are due to enzyme inhibition, competition for binding sites or diminished clearance.

When considering the safety of a drug thought should be given as to whether the drug induces its own metabolism and also if it may alter the rate of metabolism of other therapeutic drugs (Jordan et al. 1975). Sodium valproate has been shown by these authors to have no enzyme- inducing or inhibiting properties in the rat, in vitro and in vivo, at

doses up to 100 mg/kg.. When phenobarbitone (a known powerful enzyme-inducer) was also introduced, sodium valproate did not contribute any additive component of enzyme induction. However, as phenobarbitone, primidone, phenytoin, carbamazepine and pheneturide induce liver enzymes, Richens et al. (1975) believe this induction shortens the half-life of sodium valproate; an effect which is not shared by ethosuximide and the benzodiazepines.

Doses of 25-200 µg/ml. of sodium valproate were found to displace phenobarbitone slightly from protein binding sites but as initial phenobarbitone binding is low, the authors doubt its clinical significance (Jordan et al. 1975). However, as fatty acids bind at the phenobarbitone site in hepatic microsomes, it follows that sodium valproate could raise blood levels of phenobarbitone by blocking its metabolism in the liver (Wilson, in Vakil et al. 1975). In rats high doses of sodium valproate displaced diphenylhydantoin (DPH) which became significant only at concentrations of 100-200 µg/ml. in the cell (Jordan et al. 1975). Analysis of plasma sera in normal human volunteers by these authors showed that sodium valproate binds strongly to plasma (ca. 90%) but less strongly to human serum albumin (HSA , ca. 60%). This is apparently due to the fatty acid drug molecule, as up to 92% of defatted HSA binds to sodium valproate. Therefore when two drugs have a high affinity for plasma protein competition for its binding sites may result in the displacement of one drug from its binding site by another,when given in large enough doses, thus enhancing its therapeutic or toxic effect. In therapeutic doses, sodium valproate tends not to increase phenytoin plasma levels and

any recent beneficial effects on seizure control in these patients can be attributed to sodium valproate. However, given together with phenobarbitone, medication becomes potentially toxic and clinical improvement cannot be solely assigned to sodium valproate (Richens et al. 1975).

4.9. Effect on the EEG.

4.9.1. Paroxystic abnormalities.

Pentretrazol-induced seizures in rats (60 mg/kg.) have resulted in spike and wave abnormalities in the electrocorticogram two minutes before the manifestation of the tonic-clonic seizures. The spike and wave continued until the diminishing trace corresponded to a coma. Injection of DPA (200 mg/kg.) half-an-hour before the pentretrazol administration not only prevented the convulsions but also improved the characteristic trace as seen in the non-protected animal and, although rare outbursts of spike and wave and irregular slow waves occurred, the comatose phase disappeared (Lebreton et al. 1964b).

Several investigations of DPA treated EEGs in human epilepsies have often involved a large age range of chronic and intractable epileptics already on a variety of anticonvulsants. Follow up has varied between 3 months to 4 years and the overall results of EEG studies are less constant than the clinical benefits, although in the majority of cases there is a concordance between clinical and electroencephalographic cure (Fau and Garrel 1968; Miribel and Marinier 1968; Jeavons and Maheshwari 1974). Out of 24 patients with spike and wave EEG paroxyms, treatment with 800 - 1,600 mgm of DPA, added to existing medication, abolished these abnormalities in 10 cases. In the other 14 patients there were no net effects on the EEG despite a clinical improvement (DeBiolley and Sorel 1969b). When DPA was taken alone in doses up to 1,200 mgm. paroxystic abnormalities disappeared in 5 out of 17 children and were diminished in 10 others. In one patient the EEG pattern was unmodified and EEG abnormalities became worse in one other

(Miribel and Marinier 1968).

Many authors have drawn a distinction between the different types of epileptic seizures when considering the effect of sodium valproate on the EEG. Studies on patients with petit mal with the typical absence pattern of 3 c.p.s. spike and wave have usually given excellent results (Fau and Garrel 1968; Mairlot 1970). Of 50 patients treated with DPA alone, in doses up to 1,200 mgm. for children and up to 1,800 mgm. for adults, 22 cases had previously suffered with petit mal. In all but 3 patients EEG abnormalities disappeared with treatment, and in these 3 resistant cases hyperventilation and photic stimulation were required to evoke the 3 c.p.s. spike and wave (Bergamini, Mutani, Furlan and Riccio 1970). In 19 patients with typical absences, sodium valporate alone or in adjunction with other antiepileptics produced 100% clinical improvement in 16 patients and 100% EEG improvement in 15 cases (Jeavons and Maheshwari 1974). Haigh and Forsyth (1975) report that in 10 children with typical absences there were 7 who became totally fit-free on sodium valproate therapy; these patients also showed no evidence of seizure activity in their EEGs. One other patient, whose seizures were also fully controlled, still possessed 3 c.p.s. spike and wave during hyperventilation. The average dose of sodium valproate was 36 mg/kg/day. The EEG has been monitored by 12 hour telemetry in 3 adult males with a history of absence seizures. When sodium valproate was added to the existing stable and multiple anticonvulsants, 2 of the 3 patients showed a significant reduction in seizures as illustrated by diminished paroxysms in the EEG. More than 50% reduction in seizure frequency occurred in one patient although there

was a slight increase in seizure duration. In the other patient, a very short half-life and widely fluctuating serum levels of sodium valproate seemed responsible for a recurrence of seizures after a seizure-free period of a few days (Penry et al. 1975).

The EEG after sodium valproate treatment of other forms of seizure shows varying results. Bergamini et al. (1970) reported that 50% of patients with myoclonic petit mal or tonic-clonic fits still presented spike and wave with hyperventilation and photic stimulation; 5 out of 12 patients originally with petit mal and tonic-clonic attacks, who had not totally responded to DPA therapy and still had tonic-clonic seizures, all had abnormal EEGs. In small groups of patients Jeavons and Maheswari (1975) found normalisation of EEGs by sodium valproate in 40% of patients with myoclonic absences; 44% with myoclonic astatic seizures; 50% with myoclonic jerks; 70% with tonic-clonic attacks. Overall, the partial epilepsies showed less clinical and less EEG improvement than the generalised epilepsies. This was previously discovered by Völzke and Doose (1973). They found that focal changes, in particular focal sharp waves, were not affected by sodium valproate and could even increase especially in cases of multifocal sharp waves. However, focal seizures frequently improved if the EEG contained bilaterally synchronous spike and wave in addition to focal and diffuse changes.

Investigations involving frequent follow-up EEGs have noted that EEG improvement does not exactly parallel the clinical improvement but tends to be slower. Bergamini et al. (1970) observed that the clinical effects of DPA

became manifest between the fourth and twelfth day after the introduction of treatment but that the effect on the EEG was slower. The beneficial effect on the EEG by DPA in typical absence cases was delayed by 3 - 6 months after the beginning of treatment and in other forms of generalised epilepsy the spike and wave paroxysms and slow wave 'dysrhythmias' disappeared partially and slowly (Mairlot 1970). The abolition of abnormalities in the resting record has been seen over a variable period of 4 - 57 days. The disappearance of polyspike and wave paroxsms evoked by hyperventilation occurred somewhat later and those abnormalities induced by IPS were generally even more delayed. (Miribel and Marinier 1968; Jeavons and Maheshwari 1974).

It is obviously important to distinguish between the state of the EEG at rest and under these two provocative techniques. In Miribel and Marinier's (1968) sample of patients, 10 out of 17 had been photosensitive before sodium valproate therapy. On this drug 2 patients were completely cured of the photosensitive response and considerable improvement occurred in 4 other cases. The authors did not encounter aggravation of photosensitivity as can sometimes be seen with other anticonvulsants. Völzke and Doose (1973) observed in one photosensitive patient the disappearance of 'photogenic' seizures with concurrent diminishing of EEG paroxysms with IPS. Laboratory experiments with the photosensitive baboon Papio papio illustrated that intravenous administration of sodium valproate (150 mg/kg.) would block paroxysmal discharges for up to 30 minutes after injection and reduce their intensity for over one hour (Pinder et al. 1977).

In summary, sodium valproate appears to be efficacious in the treatment of patients with generalised bilaterally synchronous spike and wave EEG abnormalities particularly of the 3 c.p.s. variety. However clinical improvement tends to precede and be greater than improvement in the EEG (Völzke and Doose 1973; Jeavons and Maheshwari 1974).

4.9.2. Background EEG rhythms.

Reports on the effect of sodium valproate on the background EEG activity have been few. In 17 children treated with 200 - 600 mg/day of DPA, all showed an overall slowing down of EEG rhythms with an increased irregularity and diffuseness of theta and delta waveforms. Higher doses (above 600 mg/day) tended to produce less slow activity than lower doses with an appearance of more rapid but still irregular rhythms. The changes in the background record were constant in all patients and were usually independent of the reduction in spike and wave activity (Miribel and Marinier 1968). In this study of patients with temporal-lobe epilepsy and slow focal waves, the entire EEG now showed slowing down of all background rhythms. In similar patients, where the EEG had previously been normal, focal slow waves developed in the tempero-occipital regions or over the entire hemisphere. The authors concluded that a feature of DPA was the absence of fast rhythms and that its modifications on the background EEG paralled those of ethosuximide and the -dione group of antiepileptic drugs.

DeBiolley and Sorel (1969b) however, found no effect on the EEG either with the centrotemporal slow waves and temporal foci in 59 chronic epileptics. Similarly, Fau and Garrel (1968) noted 'infraclinical electrical paroxysms' in

the background trace of intractable patients but no modifications in the irregular basic rhythms during DPA treatment. In opposition, Mairlot (1970) reported that DPA resulted in an improvement in the background EEG of 120 patients of whom 35% received this drug as the sole anticonvulsant. It is possible that negative-findings for basic EEG rhythms arise from adverse interactions with other medication. Phenytoin toxicity proved responsible for the slowing down of waveforms, particularly in the theta and delta ranges, when this drug was combined with sodium valproate in three severely epileptic patients (Vajda et al. 1975).

4.10. Autonomic Effects.

At very high doses DPA was found to breakdown the normal temperature regulatory system of the mouse when the animal was subjected to extreme cold (Lebreton et al. 1964a). Small doses of DPA (iv) produced a transient fall in rodent blood pressure but the effect was unrelated to cholinergic, adrenergic or histaminergic mechanisms. The drug appeared to have no significant effects on the autonomic nervous system in the absence of a direct effect upon the heart, respiration or nictitating membrane (Swinyard 1964). Similarly, other animal studies have found a lack of DPA action on respiration, arterial blood pressure, renal function, and body temperature (Olive et al. 1969; Reckitt and Coleman 1973). A survey by Pinder et al. (1977) found no hepatic, cardiac, or renal contraindications attributable to sodium valproate.

4.11. Clinical Trials.

The majority of studies of the clinical effects of sodium valproate have been uncontrolled and involve observations on mainly severely epileptic patients. The duration of follow up varies widely from a few weeks to several years and the trend has been for the addition of sodium valproate to previously existing medication with resultant decrease in dosage of these drugs, depending on subsequent clinical improvement and the occurrence of side effects due to drug interactions. Adult patients, on average, received around 1,200 mgm. of sodium valproate daily and children about 30 - 40 mg/kg/day in divided doses (Penry et al. 1977). Only a few studies have administered sodium valproate alone to appreciable numbers of patients; 73% (Haigh and Forsyth 1975); 17% (Hassan et al. 1975); 35% Mairlot (1970); an entire sample of 70 patients (Price 1975).

Many authors have assessed the clinical effects of sodium valproate as percentage reduction in fit frequency according to seizure type. In the following account the most usual forms of generalised and partial epilepsies are reviewed. Discrepancies between authors may partly arise due to individual interpretations of significant and satisfactory responses. When conducting open or uncontrolled trials it is importment to determine a baseline of seizure frequency in relation to the duration of the intended drug investigation.

4.11.1. Absence seizures.

Many authors report excellent results with sodium valproate in the treatment of typical and atypical absence seizures and in particular those characterised by 3 c.p.s. spike and wave abnormalities in the EEG (Morice, Pascalis

and Gross 1968; de Biolley and Sorel 1969a, b; Völzke and Doose 1973; Jeavons and Clark 1974; Jeavons and Maheshwari 1974; Haigh and Forsyth 1975; Heathfield et al. 1975; Richens et al. 1975). Prior to sodium valproate many of the patients investigated were resistant to existing antiepileptic medication, with seizures occurring in the order of four per month to over twenty seizures per day (Jeavons and Clark 1974; Heathfield et al. 1975). In general sodium valproate was added to the current medication but this was later gradually decreased. Often the reduction in seizure frequency was spectacular and in the majority complete suppression of absences occurred at a critical dose of sodium valproate (Bergamini et al. 1970; Völzke and Doose 1973; Jeavons and Clark 1974; Heathfield et al. 1975). Improvement was usually apparent within a few days but at times treatment was necessary for several weeks to achieve optimum control (Reckitt and Coleman 1973). In one group of 16 patients with atypical absences, 69% were fully controlled with a normal EEG in less than one month (Jeavons and Maheshwari 1974).

A survey of the literature up to 1975 (Table 4.1.) of patients treated with sodium valproate for absence seizures shows that improvement was achieved in 84% of patients, 64% showing either a dramatic reduction in seizure frequency or total suppression of attacks. The result reaches statistical significance at the 1% level.

In a few cases where sodium valproate alone does not produce significant improvement the addition of trimethadione, methsuximide or ethosuximide, even when these drugs have previously been ineffective, will considerably reduce or abolish seizures (Mairlot 1970; Völzke and Doose 1973; Haigh and Forsyth 1975). Sodium valproate has proved to be more

Author	Number of cases	Decrease in seizure frequency		
		100 - 75%	75 - 30%	< 30 %*
Reckitt & Coleman 1973	275	166	57	52
Volzke & Doose 1973	34	23	9	2
Jeavons & Clark 1974	17	14	1	2
Barnes & Bower 1975	1	1	0	0
Haigh & Forsyth 1975	10	9	0	1
Heathfield et al. 1975	8	8	0	0
Hassan et al. 1975	8	5	2	1
TOTAL	353	226	69	58
%	100	64	20	16
χ^2	= 150 · 12 P < 0 · 001 df = 2 · (S)			

Table 4.1. Result survey of the effect of Sodium Valproate on Absence Seizures

* Includes patients unchanged and deteriorated

Author	Number of cases	Decrease in seizure frequency		
		100 - 75%	75 - 30%	< 30 %*
Reckitt & Coleman 1973	342	161	73	108
Volzke & Doose 1973	29	22	2	5
Jeavons & Clark 1974	19	10	6	3
Grant & Barot 1975	59	18	23	18
Haigh & Forsyth 1975	11	4	0	7
Heathfield et al. 1975	3	2	0	1
Hassan et al. 1975	10	4	3	3
TOTAL	473	221	107	145
%	100	47	22	31
χ^2	= 42 · 74 P < 0 · 001 2 df. (S)			

Table 4.2. Result survey of the effect of Sodium Valproate on Tonic-clonic Seizures

effective than the succinimides in the treatment of absence seizures and addition will not produce the psychic problems as seen with high doses of ethosuximide over long periods. Consequently there is growing opinion that sodium valproate is the new drug of choice in the treatment of this form of epilepsy in both children and adults (Bergamini et al. 1970; Grant 1976; Haigh and Forsyth 1975; Heathfield et al. 1975).

4.11.2. Tonic-clonic seizures.

There is some controversy over the effect of sodium valproate therapy on tonic-clonic attacks. Morice et al. (1968) reported that DPA did not seem to act upon this type of epilepsy, and recently a study of 36 intractable patients over 1 - 2 years proposed that sodium valproate was of less value in treating tonic-clonic fits. Although, two children with these fits alone and fast spike and wave variant in the EEG responded well to this new drug (Heathfield et al. 1975). Even doses of 1.8 g/day of sodium valproate proved ineffective in 7 of 11 cases of tonic-clonic epileptics, whereas the other 4 patients had responded with a 90% reduction in attacks. However, it was evidential that the majority of unimproved patients had cortical damage (Haigh and Forsyth 1975).

When determining the activity of sodium valproate on tonic-clonic fits it is important to distinguish between primary generalised attacks, where there is no clinical or EEG evidence of organic cerebral damage (the interictal EEG being characterised by bilaterally synchronous 3 c.p.s. spike and wave or polyspike and wave complexes), and secondary generalised attacks which may occur through the build up of partial epileptic or focal attacks. Here the interictal EEG shows diffuse cerebral damage with discharges of sharp waves and slow waves. Hassan et al. (1975) achieved full remission

of attacks in 22% of patients with primary generalised seizures and in 6% of patients with secondary generalisation treated with sodium valproate alone or with other anticonvulsants. The frequency of fit reduction by more than half was 50% and 63% of these patients respectively. A large survey of 224 children with severe epilepsy found good results with primary tonic-clonic attacks as addition or substitution of therapy with sodium valproate produced more than a 90% reduction in fits for 82% of such cases. Nocturnal tonic-clonic attacks and tonic-clonic fits with focal signs did not respond well. In the latter, only 21% of patients showed a significant improvement and no response occurred in 42% (Barnes and Bower 1975). In agreement are the findings of Völzke and Doose (1973) who found that only 25% of patients with nocturnal fits or tonic-clonic attacks with focal signs became seizure free.

Generally, favourable results have been obtained with sodium valproate in the treatment of tonic-clonic seizures although in some cases discontinuation of other drugs has not always been possible and maintenance of low level doses of barbiturates or hydantoins have been required to maintain optimal control. Disappearance of seizures sometimes occurred within one month and lasted up to 2 years (Dumon-Radermecker 1969; Mairlot 1970; Reckitt and Coleman 1973; Grant 1976).

It appears therefore that sodium valproate is efficacious particularly in patients with primary generalised (idiopathic) tonic-clonic seizures with regular spike and wave paroxysms in the EEG (Bergamini et al. 1970; Völzke and Doose 1973). Most investigations have been on chronic epileptics, resistant for years to maximal doses of the usual anticonvulsants and many have found a considerable drop in

seizure frequency in at least 50% of patients (Jeavons and Clark 1974; Jeavons and Maheswari 1974; Hassan et al. 1975). Table 4.2 shows that of 437 reported cases in the literature, 47% achieved a significant improvement with sodium valproate and that overall 69% of the patients derived some benefit from this therapy.

4.11.3. Myoclonic epilepsy.

Dumon-Radermecker (1969) was the first to report that DPA gave 'modest results' in the treatment of progressive myoclonic epilepsy (Unverricht-Lundborg syndrome). This beneficial effect was observed by Völzke and Doose (1973) in 2 out of 3 patients with myoclonic syndrome in the course of degenerative cerebral disease. A review by Reckitt and Coleman (1973) found that sodium valproate had been used with limited success in the treatment of myoclonic jerks and recommended combined therapy with phenobarbitone. However, later studies show more favourable results. Jeavons and Clark (1974) report that myoclonic epilepsies respond well to sodium valproate. Of 5 patients with bilateral myoclonic jerks, all became fully controlled.

Authors sometimes fail to differentiate between the differing types of myoclonic epilepsies and as numbers are generally small it is difficult to assess the efficacy of sodium valproate on the particular disorders. However, Jeavons and Maheshwari (1974) found that nearly 50% of various types of myoclonic cases became fit-free after treatment. A substantial effect was noted by Barnes and Bower (1975) and in two patients, purely with myoclonic jerks, one became fully controlled and the other showed more than 80% remission of seizures (Grant and Barot 1975). A summary of 21 cases reported in recent literature can be seen in Table 4.3.

Author	Number of cases	Decrease in seizure frequency		
		100–75%	75 – 30%	< 30 %*
Volzke & Doose 1973	3	0	2	1
Jeavons & Clark 1974	10	9	1	0
Barnes & Bower 1975	3	1	1	1
Grant & Barot 1975	3	2	1	0
Hassan et al. 1975	2	2	0	0
TOTAL	21	14	5	2
%	100	67	24	9
χ^2	$=11\cdot14$	$P<0\cdot01$	$df=2$	(S)

Table 4.3. Result survey of the effect of Sodium Valproate on Myoclonic Jerks

Author	Number of cases	Decrease in seizure frequency		
		100 – 75%	75 – 30%	< 30 %*
Volzke & Doose 1973	10	3	2	5
Jeavons & Clark 1974	4	0	3	1
Grant & Barot 1975	2	1	0	1
Harwood & Harvey 1975	29	7	15	7
Hassan et al. 1975	11	2	5	4
Richens et al. 1975	4	0	2	2
TOTAL	60	13	27	20
%	100	22	45	33
χ^2	$=4\cdot90$	$P=0\cdot1$	$df=2$	(NS)

Table 4.4. Result survey of the action of Sodium Valproate on Focal Epilepsy

* Includes patients unchanged and deteriorated

illustrating that sodium valproate is significantly effective in reducing seizures by over 25% in over half the patients and overall has beneficial activity in 91% of cases with myoclonic jerks. Sodium valproate could well be considered as the first drug of choice in myoclonic epilepsy (Grant 1976).

4.11.4. Atonic/Akinetic seizures.

Results for atonic and akinetic seizures have often been pooled by authors. In the few reported patients with myoclonic petit mal and irregular EEG paroxysms of spike and waves, Bergamini et al. (1970) achieved a clinical cure in 4 out of 6 patients, although hyperventilation in conjunction with IPS still produced polyspike and wave discharges. DPA controlled myoclonic petit mal in all 3 patients studied by Völzke and Doose (1973) and they postulated that this treatment was especially effective when started early, before the occurrence of brain damage as a result of seizures. In three other children with myoclonic/akinetic epilepsy no response was found (Haigh and Forsyth 1975). In a combined group of 22 adults and 7 children with akinetic/atonic seizures diminuation of attacks by over 50% was accomplished in 15 cases. Although the adults showed no significant change in akinetic seizures, the main reduction in children was 75%. A review of reported cases by Pinder et al. (1977) illustrates that only about one third of patients reach optimal control, whereas nearly half either obtain slight improvement or no change in their epileptic condition.

4.11.5. Partial seizures with elementary symptomatology.

Völzke and Doose (1973) report complete success of sodium valproate in only one of 6 children suffering with drop seizures of focal or multifocal origin. One other child

deteriorated both clinically and in the EEG. In 4 patients with other forms of focal seizure, 2 became seizure free. It was noted that improvement occurred in those cases where the EEG also contained bilaterally synchronous spike and wave in addition to focal and diffuse activity. However, in every case focal EEG abnormalities remained unchanged. In 4 patients with focal motor seizures more than a 50% improvement occurred in 3 cases (Jeavons and Clark 1974). Sodium valproate was moderately effective in the treatment of intractable focal epileptics during an uncontrolled trial by Harwood and Harvey (1975). A 50% reduction in attacks occurred in 52% of patients and 90% improvement was seen in a further 24% of the cases. However, the authors point out that the duration of follow-up varied amongst patients who tended to be lax in keeping a record of their fits. Also no correction was made for patients who suffered simultaneously from a variety of seizure-types eg. secondary generalised tonic-clonic attacks were included in this assessment.

Sodium valproate was given as the sole anticonvulsant to a large sample of neurosurgical patients where 77% suffered from focal attacks with or without secondary generalisation. Similarly, 10% had psychomotor attacks and 13% had primary generalised epilepsy (Price 1975). Unfortunately the results are discussed according to the previous fit frequency, and not to seizure type. However, 87% of the 'high-risk' group maintained complete freedom from seizures for at least 3 months. All other 'risk' groups achieved full control in all patients. Dosage of sodium valproate was high in this study, the majority requiring daily dosages of up to 2 gm. but in some cases up to 5 gm. were necessary. Hassan et al.

(1975) found that in a group of patients with partial seizures with simple symptomatology, 9% became seizure-free and 36% experienced a reduction by over half of their initial seizure frequency. No benefit occurred in another 36% of patients.

Table 4.4 shows the results of 5 uncontrolled and one controlled trial (Richens et al. 1975) for a total of 60 patients. Only 22% of cases responded with at least a 75% reduction in seizure frequency. A further 45% of patients underwent a reasonable improvement but one third of the group showed either slight improvement, no change, or deterioration. There is no significant difference between the levels of seizure reduction. Reckitt and Coleman (1973) concluded that sodium valproate has a limited value in the treatment of focal epilepsies, viz. focal motor seizures where phenobarbitone remains the drug of choice. However, when sodium valproate does not control partial seizures well, improvement may occur by the addition of carbamazepine (Harwood and Harvey 1975).

4.11.6. Partial seizures with complex symptomatology.

As with investigations on other forms of seizures, sodium valproate has mainly been used as an adjunctive to existing medication of refractory patients. Results with psychomotor epilepsy, in any single study, may be diverse. DeBiolley and Sorel (1969a) found excellent results in 4 out of 10 patients but completely negative findings in another 4 cases. Dumon-Radermecker (1969) noted that DPA was useful in the treatment of confusional psychotics as regards its beneficial effect on the 'absences and psychotic phenomena' but with other forms of temporal lobe epilepsy results varied widely. Although psychomotor seizures became well controlled in 50% of a series by Völzke and Doose (1973), three-quarters of these seizure-free patients still showed generalised spike

and wave plus diffuse EEG abnormalities.

Many authors observed little or no response in the treatment of psychomotor epilepsy even with a higher than average daily dose of sodium valproate, 1,200 mgm. - 3,200 mgm. (Jeavons and Clark 1974; Haigh and Forsyth 1975; Harwood and Harvey 1975; Heathfield et al. 1975; Richens et al. 1975). However, a reduction in seizure frequency tended to occur in patients with secondary generalised fits and, regardless of any direct clinical benefit, it was often possible to reduce other anticonvulsants and improve their mental outlook (Jeavons and Clark 1974).

In one uncontrolled study children responded better to treatment than adults with mean reductions in seizure frequency of 82% and 51% respectively (Grant and Barot 1975). A controlled trial using a fixed dose of 1,200 mg/day or placebo during an 8 week double blind cross-over failed to give a therapeutic response in the few patients with temporal lobe lesions (Richens et al. 1975). It may be possible that any age effects are due to the greater compensatory nature of younger brain matter, than of adults, when specific lesions are present. Sodium valproate has rarely proven successful in treating psychomotor epilepsy in the brain damaged patient and in symptomatic epileptics (partial or generalised) (Heathfield et al. 1975).

A survey of results in the literature (Table 4.5.) illustrates the conservative action of sodium valproate on psychomotor seizures. A considerable effect is seen in only 29% of cases with some degree of benefit in just over half (59%) and very little change or deterioration in just under half the patients.

Author	Number of cases	Decrease in seizure frequency		
		100 – 75%	75 – 30%	< 30 %*
Reckitt & Coleman 1973	168	52	55	61
Volzke & Doose 1973	8	4	0	4
Jeavons & Clark 1974	10	0	2	8
Barnes & Bower 1975	5	0	2	3
Grant & Barot 1975	45	13	16	16
Haigh & Forsyth 1975	5	0	0	5
Harwood & Harvey 1975	65	21	18	26
Heathfield et al. 1975	7	3	1	3
Hassan et al. 1975	18	3	6	9
TOTAL	331	96	100	135
%	100	29	30	41
χ^2	= 8·35	P < 0·02	df = 2	(S)

Table 4.5. Result survey of the action of Sodium Valproate on Psychomotor Seizures

* Includes patients unchanged and deteriorated.

4.11.7. Mixed seizures.

Many patients suffer from more than one form of epilepsy often requiring the combination of two or more antiepileptic drugs. This can lead to problems of unpleasant side-effects, through drug interaction, and difficulties in assessing the efficacy of individual therapeutics. As previously mentioned sodium valproate has the advantage of allowing removal or reduction of the previous medication to some extent. Even when its use as a major antiepileptic drug is not viable, in combination as a minor-epileptic it appears to augment the power of other anticonvulsants or provide beneficial collateral effects on the patients character (Bergamini et al. 1970; Jeavons and Clark 1974).

When tonic-clonic and absence seizures occur together, sodium valproate has been effective in most cases. In a group of 12 patients, 7 became fully cured, but the other 5 still showed persistence of tonic-clonic seizures and their EEGs remained abnormal with hyperventilation during IPS (Bergamini et al. 1970). In those cases in which a major attack occurs after a build up of the minor (absence) seizure, controlling the latter usually prevents the tonic-clonic attack (Heathfield et al. 1975). These authors achieved considerable improvement in 7 patients who were also taking phenytoin together with sodium valproate. Combination with phenobarbitone has proved effective in many cases of this mixed form of epilepsy which in general is resistant to medication (Reckitt and Coleman 1973). Out of 246 cases treated with sodium valproate excellent control was maintained in 51% and overall 85% of patients responded to treatment (see Table 4.6.).

As regards other polymorphic seizures, Mairlot (1970) reported that more adults compared to children show salutary

Author	Number of cases	Decrease in seizure frequency		
		100-75%	75 - 30%	< 30 %*
Reckitt & Coleman 1975	214	106	77	31
Haigh & Forsyth 1975	4	2	0	2
Heathfield et al. 1975	7	7	0	0
Hassan et al 1975	21	10	8	3
TOTAL	246	125	85	36
%	100	51	34	15
χ^2	= 48·46	P < 0·001	df = 2	(S)

Table 4.6. Result survey of the effect of Sodium Valproate on Mixed Tonic - clonic / Absence Seizures.

Author	Number of cases	Decrease in seizure frequency		
		100-75%	75 - 30%	< 30 %*
Barnes & Bower 1975 (Mixed)	10	4	3	3
Haigh & Forsyth 1975 (Myoclonic / akinetic)	3	0	0	3
Heathfield et al. 1975 (Temporal lobe & tonic clonic)	5	0	1	4
Hassan et al. 1975 (Mixed)	19	6	11	2
TOTAL	37	10	15	12
%	100	27	41	32
χ^2	= 1·03	P = 0·7	df = 2	(NS)

Table 4.7. Result survey of the action of Sodium Valproate on other forms of Mixed Seizures

* Includes those patients unchanged & deteriorated.

progress on sodium valproate. However, the effect was unstable but again allowed dosage reduction of other drugs. The overall results with children were less favourable as the author regarded improvement in behaviour as well as decrease in seizures as a criterion, but EEG improvement was obvious in this age range. A double-blind controlled study on 20 severely epileptic patients with major and minor seizures (absence, adversive, focal and psychomoter) produced a significant reduction in all seizures, except in some cases of temporal lobe lesion. The frequency of major fits during sodium valproate treatment was on average 35% of the frequency on placebo and similarly 57% for minor seizures (Richens et al. 1975). Conflicting results have been found by other authors in uncontrolled investigations (Table 4.7). Although the global result shows lack of significance between the degree of improvement, seizures are ameliorated in 68% of patients.

4.11.8. Childhood epilepsy.

Myoclonic astatic epilepsy (Lennox syndrome) is the most resistant form of childhood epilepsy to medication. DeBiolley and Sorel (1969b) found that DPA was ineffective for this condition. Contrary results were found by Dumon-Radermecker (1969) and Jeavons and Clark (1974). In the latter study of 11 retarded patients with myoclonic astatic epilepsy, 3 became fully controlled, 3 improved by over 50%, and the remainder showed some improvement. The average duration of illness in these patients was 8 years and in the light of the refractory nature of this condition the authors considered the results as remarkable.

Good results have been obtained in the treatment of infantile myoclonic epilepsy with hypsarythmia (West's syndrome) in cases which failed to respond to ACTH. Olive

et al. (1969) achieved excellent results in 5 out of 10 infants. In 3 of the group clinical signs disappeared, but the EEG abnormalities persisted. Sodium valproate has been shown to have an immuno-stimulant action (Dumon-Radermecker 1969) and can be used in association with standard ACTH therapy as it potentialises the anti-inflammatory effect and prolongs corticoid treatment without its problems. Out of 31 reported cases Reckitt and Coleman (1973) determined that sodium valproate treatment was dramatic in 16 (52%).

Sodium valproate had no action on neonatal encephalopathies (Dumon-Radermecker 1969), but investigations into the treatment of post-encephalitic epilepsy in general gave good results in 45% and a moderate response in 11% of cases. Generalised convulsive epilepsy in the infant responded similarly to sodium valproate as in the youth and adult (Olive et al. 1969).

4.11.9. Summary.

It is evident that sodium valproate is particularly effective in children and adults with idiopathic epilepsy i.e. major generalised seizures, typical and atypical absences, myoclonic epilepsy, which is characterised by bilaterally synchronous spike and wave or polyspike and wave complexes in the EEG. Partial seizures and symptomatic epilepsy with focal features and/or evidence of cerebral damage do not respond well to sodium valproate. However, where optimal control is not achieved on this drug alone, addition of reduced doses of previous medication usually improves seizure frequency and normalises those intractable patients previously suffering from high levels of toxicity through multiple chemotherapy.

A review of many forms of epilepsy, studied at

various neurological and special centres, on the effect of sodium valproate on seizure frequency, showed that within 2 to 12 months on dosages of 400-1,800 mg/day, 21% of patients had become fit-free, 32% had more than a 40% reduction of seizures, 25% improved to some extent and 22% were unbenefitted by the treatment (Reckitt and Coleman 1973). A comprehensive review of 2,031 patients was conducted by Pinder et al. (1977). Although duration of therapy and dosage varies widely between and within the analysed studies, 899 (44%) of patients experienced a reduction in seizure frequency of at least 75%, 509 (25%) improved by 33-75%, and 623 (31%) were considered as failures of sodium valproate treatment.

4.12. Side Effects and Contraindications.

4.12.1. Tetragenicity.

Initial studies by Dumon-Radermecker (1969) found no evidence of a teratogenic action of sodium valproate in rodents and rabbits. However more recent reports indicate that placental transfer does occur and is capable of producing dose related dysmorphogenic effects in animals. Whittle (1975) reported that kidney agenesis, encephaloceles, ablepharia, rib and vertebrae fusions and cleft palate were the most common defects in rabbit, rat, and mouse although species variations occurred. In rats the teratogenic effect was dose related; in mice the abnormalities were spread more widely through the dose range; in rabbits the number of intra-uterine deaths increased with dose, and foetal abnormalities were seen only at doses near to those producing death. The target organs in rabbit and rat were different from those affected by phenytoin but in the mouse the responses to phenytoin and sodium valproate were essentially similar.

Estimating the incidence of teratogenicity in humans is difficult as reports are few in number and usually the patient has been on combined medication during pregnancy. Hassan et al. (1975) were unable to detect any indication of teratogenicity in humans. Of 7 mothers, on sodium valproate, all produced healthy offspring when coming to term (Whittle 1975). There was one incidence of soft tissue foetal abnormality (hairlip, cleft palate, with low birth weight) where sodium valproate had been given to the mother for one week at two months before delivery. However during pregnancy she had been taking phenobarbitone, sulthiamine, and ethosuximide (Pinder et al. 1977).

4.12.2. Behaviour.

Many epileptics suffer with character and behaviour problems in conjunction with their predisposition to seizures. Secondary effects of anticonvulsants particularly with multiple medication are largely responsible for these behaviour problems. The general opinion from sodium valproate studies is that many patients become more alert, lively, self-confident and competent. (Fau and Garrel 1968; Dumon-Radermecker 1969; Bergamini et al. 1970; Heathfield et al. 1975; Vajda et al. 1975). Behaviour troubles are primarily seen in epileptic children and young adults up to 21 years of age (Hassan et al. 1975). The authors found that although about one third of their patients were cured behaviourally 50% of that success rate was unstable, whereas slightly more than one third of a group of children (N = 14) improved favourably and in all but one child benefit remained. The lack of sedative, anorexigenic or enervating effects of sodium valproate renders it useful in childhood epilepsies as intellectual function is unimpaired and in some cases school performance improves (Dumon-Radermecker 1969; Mairlot 1970; Barnes and Bower 1975; Hassan et al. 1975; Pinder et al. 1977).

Improvement in behaviour generally accompanies a diminution or suppression of seizures (Hassan et al. 1975), although in some cases improvement in character may precede the clinical progress (DeBiolley and Sorel 1969a). Mental stimulation can occur with sodium valproate alone or in the absence of any changes in previous drug dosage (Mairlot 1970; Jeavons and Clark 1974; Grant and Barot 1975; Hassan et al. 1975; Timpany 1975).

Deterioration in behaviour with aggressiveness and hyperkenesis may occur especially in children. One survey reported an incidence of 0.9% in over 3,000 patients of

worsened behaviour which was increased to 2.4% in a sample of 251 children under 16 years old (Noronha and Bevan 1975). However many instances of this undesirable effect occur in children with a history of hyperactivity or in retarded patients (Barnes and Bower 1975; Haigh and Forsyth 1975); in other cases reducing the dosages of other medication will control this problem. In two patients with aggravated behaviour, both were receiving combined anticonvulsants (Mairlot 1970). Jeavons and Clark (1974) reported that behaviour disorders in 3 children disappeared as a result of reducing primidone dosage and that a reduction in acetazolamide improved overactivity. It is probable that hyeractivity in some children is their reaction to feeling so well after being previously severely restricted by their epileptic condition.

4.12.3. Effect on blood platelets.

The effect of sodium valproate on blood platelet function and number is questionable. In a small group of 5 patients, Sutor and Jesdinsky-Buscher (1974) found prolonged bleeding times in 4 cases. This was associated with defective platelet aggregation. Dosage was believed to play a significant role as the only patient who had thrombocytopenia was receiving 1.5 g/day of sodium valproate alone whilst the other 3 asymptomatic cases received 450 - 900 mgm. daily in conjunction with other drugs in 2 cases. Another case of thrombocytopenia was of a 6 year old boy taking 1,600 mgm. of sodium valproate only which produced plasma serum levels of 244 µg/ml. His spontaneous bruising was also associated with a prolonged bleeding time and a fall in the platelet count. However, other coagulation tests were normal and in vitro tests showed no abnormalities in platelet

aggregation. Withdrawal of sodium valproate caused a rapid increase in platelet count during 48 hours and was normalised within one week (Espir et al. 1975).

In 6 normal subjects inhibition of secondary platelet aggregation was studied in vitro in the presence of therapeutic and up to twenty-five times the therapeutic levels of sodium valproate (Richardson, Fletcher, and Jeavons 1975). Inhibition occurred in half of these subjects at a therapeutic level and was particularly marked in the presence of phenobarbitone and asprin. A similar inhibitory effect on platelet aggregation occurred in 6 out of 23 epileptic patients treated with 600 - 1,400 mg/day of sodium valproate, 17 of which received sodium valproate as the sole anticonvulsant. However, there was no statistical significance in defective platelet function between patients on sodium valproate alone and patients taking combined medication. In no patient was bleeding time prolonged and the authors concluded that although there was no apparent clinical significance of sodium valproate on platelet function caution should be taken in prescribing asprin and other drugs with anti-coagulatory effects for patients on sodium valproate.

A few cases of haemostatic complications have been reported in the literature and platelet dysfunction caused by sodium valproate cannot be entirely out-ruled (Espir et al. 1975; Pinder et al. 1977).

4.12.4. CNS effects.

A commonly reported side-effect of sodium valproate therapy is drowsiness or sedation in patients. It is difficult to determine the exact hypnotic effect of this drug as it is often given in combination with other antiepileptics. In the majority of cases sleepiness occurs during the initial

stages of therapy when sodium valproate is being introduced. Drowsiness is usually transient and either disappears spontaneously (Bergamini et al. 1970; Richens et al. 1975) or with a reduction in dosage of other drugs, in particular barbiturates, primidone, hydantoins, and benzodiazepines (DeBiolley and Sorel 1969a,b; Dumon-Radermecker 1969; Völzke and Doose 1973; Jeavons and Clark 1974; Barnes and Bower 1975; Espir et al. 1975; Harwood and Harvey 1975; Heathfield et al. 1975). Sodium valproate raises the serum blood levels of some drugs, viz: phenobarbitone (see section 4.8) and is therefore capable of potentialising their side effects (Mairlot 1970; Barnes and Bower 1975; Haigh and Forsyth 1975). When 1,200 mgm. of sodium valproate was used as an adjunctive in 20 patients, an average rise of 27% was observed in serum levels of phenobarbitone (Richens et al. 1975). Although few studies have involved sodium valproate as the sole anticonvulsant, stupor has rarely been observed with the drug alone (Völzke and Doose 1973). In 2 patients on 60 mg/day and in 2 children accidentally dosed with 100 mg/kg/day by their mother no sedative or adverse reaction occurred. A review of 3,328 patients by Noronha and Bevan (1975) found an overall incidence of 5.1% for drowsiness of which only 0.2% could be directly attributed to sodium valproate alone. However, reduction in other anticonvulsants or slow re-introduction of sodium valproate has proved ineffective in a small number of patients who subsequently withdrew from their trial (Espir et al. 1975; Price 1975).

Three incidents of unexplained coma were seen by Harwood and Harvey (1975) and two by Völzke and Doose (1973). In the latter study the authors claimed that combined medication did not appear responsible due to favourable

tolerance during several weeks previous to the onset of coma. However they did not allow for any possible build up of these other drugs or sodium valproate. On withdrawal of sodium valproate consciousness returned in the two children. It was noted that coma began during severe infection in one patient and measles in the other.

Ataxia and nystagmus have also occurred when sodium valproate has been added to other anticonvulsants, viz. pheneturide, carbamazepine, ethotoin, phenytoin, phenobarbitone, primidone, and subsequently disappeared on reduction or withdrawal of these other drugs (Jeavons and Clark 1974; Barnes and Bower 1975; Haigh and Forsyth 1975; Richens et al. 1975).

There have been a few reports of tremor, usually fine to medium of the hands and associated with high dosages (ca. 120 µg/ml.) of sodium valproate (Espir et al. 1975; Price 1975). Although Harvey and Harwood (1975) finding tremor in 8 out of 9 patients believed it to be an idiosyncratic reaction. The incidence of tremor between the various drug trials was related to how closely authors enquired of their patients. Tremor in one patient only occurred with sodium valproate plus carbamazepine (Timpany 1975). In a sample of 92 patients, 6 acquired tremor of which 2 patients were taking sodium valproate alone (Espir et al. 1975).

The combination of carbamazepine with sodium valproate produced diplopia in two patients already showing additional side effects of increased appetite or vomiting (Hassan et al. 1975). It is possible that sodium valproate may aggravate migraine although information is scanty. Barnes and Bower (1975) observed that 3 out of 24 children

complained of headaches after starting sodium valproate. In 2 cases the headaches ceased after temporary withdrawal from the trial. An increase in the severity of migraine was noted by Harwood and Harvey (1975) and this reaction definitely occurred in 4 reported cases (Heathfield et al. 1975).

4.12.5. Gastro-intestinal effects.

Nausea, vomiting, and indigestion were the most commonest complaints associated with the administration of sodium valproate. Many authors found these troubles transient and that they usually occurred when patients did not take the tablets with meals or with large amounts of fluid (Fau and Garrel 1968; Dumon-Radermecker 1969; Mairlot 1970; Jeavons and Clark 1974; Espir et al. 1975; Hassan et al. 1975; Richens et al. 1975). Gastro-intestinal irritation is probably dose-dependent (Barnes and Bower 1975; Haigh and Forsyth 1975) as sodium valproate forms the free-acid in the stomach which causes a stimulant action of the musculature lining (Meijer and Meinardi 1975; Dumon-Radermecker 1969). Occasionally persistent vomiting or diarrhoea necessitates withdrawal of sodium valproate (Miribel and Marinier 1968; Hassan et al. 1975) and the patient may require hospilisation. Infants appear to resist adverse digestive reaction (Olive et al. 1969) and nausea seems more pronounced in older patients (Barnes and Bower 1975). Noronha and Bevan (1975) found an incidence of gastric intolerance in 9.3% of over 3,000 patients, of which the complaints were transient in 7.9% and severe in 1.4% resulting in withdrawal of sodium valproate. However, for 251 children under 16 years the overall incidence increased to 22.3% being transient in 20.3% and causing termination of therapy in 2%. In some cases it

was evident that sickness results from combined medication with other drugs, viz. phenytoin or carbamazepine (Mairlot 1970; Jeavons and Clark 1974; Hassan et al. 1975).

Earlier studies combated gastro-intestinal symptoms with antacids or spasmolytics (DeBiolley and Sorel 1969a,b; Bergamini et al. 1970; Völzke and Doose 1973). However, these mainly mild secondary effects can be avoided by not taking sodium valproate on an empty stomach and incidence should gradually decline with the introduction of enteric-coated and slow release preparations.

4.12.6. Changes in appetite.

Sodium valproate appears to have contrary effects on appetite as anorexia and increased appetite have been reported. Loss of appetite may be associated with vomiting and occasional or prolonged anorexia (Miribel and Marinier 1968; Dumon-Radermecker 1969; Mairlot 1970). In 24 children Barnes and Bower (1975) observed that 4 patients became anorexic for a few days during the introduction of sodium valproate. At high dosage, 2 young patients had a prolonged suppression of appetite without nausea. In other patients appetite improved when previous anticonvulsants were reduced. Therefore the authors believe that decrease in appetite is directly related to sodium valproate and with such children growth patterns should be monitored. However, in another group of predominately children up to 15 years (85%), 4% acquired an increased appetite resulting in weight gain. Improvement in appetite occurred in 20% of 90 patients with resultant gain in weight in one third of these affected cases. Only one patient was taking sodium valproate as the sole anticonvulsant (Hassan et al. 1975). It was postulated that better control of seizures would create a feeling of

well-being and thus encourage weight increase. Over 14 months of treatment 6 of 70 patients had gained between 5 - 20 kgm. of body weight through increased appetite (Price 1975). In the last two studies it is interesting that 69% of patients gaining weight were female. Change in appetite does not appear to be a major problem with sodium valproate as the overall incidence was 1.3%, of which 0.6% had increased appetite and 0.7% had less desire for food (Noronha and Bevan 1975).

4.12.7. Hair loss.

Initially reports of hair loss were sporadic but an incidence of 15% was reported by Jeavons and Clark (1974) as a result of careful enquiry of patients. Hair loss was minor and transient in 2 of 24 patients after 2 and 5 months of sodium valproate treatment, although one patient had previously suffered hair loss with other changes in medication (Barnes and Bower 1975). Similarly, Haigh and Forsyth (1975) observed a mild hair loss in a female patient and did not alter the sodium valproate dosage. In general, transient hair loss occurs in 0.5% of patients, is of little concern to the patients and does not require reduction of dosage or withdrawal of the drug (Noronha and Bevan 1975). Alopecia was confirmed dermatologically in 6 of 15 patients who had reported hair loss. At the time all 6 were also receiving phenytoin and no hair loss occurred with sodium valproate alone (Jeavons and Clark 1974). Völzke and Doose (1973) had previously reported hair loss in only 2 of 16 patients and could not establish whether responsibility lay with sodium valproate. One patient complaining of hair loss and drowsiness withdrew from a drug trial but, as indicated by the drowsiness, it is possible that combined medication and

not sodium valproate alone was responsible for the alopecia (Heathfield et al. 1975). Temporary hair loss occurred in 5 of 92 patients but was severe in 2 siblings only receiving sodium valproate (Espir et al. 1975).

Thinning of hair may be a sign that sodium valproate has an effect on rapidly dividing cells (Scott et al. 1975). Although only 3 of 90 patients suffered hair loss at doses of 1,200 - 1,800 mg/day, it had a delayed onset of 1 - 7 months and in one patient persisted for over a year. In the other 2 cases hair loss ceased after 3 - 7 months but without accompanying re-growth of hair. Body hair was unchanged but in the men facial hair grew more strongly (Hassan et al. 1975). The authors also observed a coarsening of hair texture and Barnes and Bower (1975) reported improved hair texture in three children. Hair curliness has been observed in a few patients after a variable delay and may eventually grow out (Jeavons, Clark and Harding 1977).

4.12.8. Additional effects and summary.

A few reports comment on the occurrence of skin irritation. This was reported by one patient on 1 gm. and was dose-dependent in another at dosage above 2 g/day (Price 1975). Similar effects were observed in 2 other patients but in neither case did skin eruptions develop. Complaints of oesophageal irritation (Price 1975) are probably the result of effects similarly linked with gastro-intestinal problems. Nocturnal eneuresis reappeared in 3 patients (Mairlot 1970) and occurred in 2 of 36 patients on valproate therapy (Heathfield et al. 1975). It was attributed to increased depth of sleep rather than nocturnal epilepsy.

Sodium valproate may potentiate the side effects of some drugs or, when in combination with other drugs

particularly at high dosage, create secondary reactions previously unseen. However, alone or in conjunction with low doses of other antiepileptics it is a safe drug and has minimal adverse effects. The most common complaint is gastro-intestinal irritation which can be corrected and is transient. Unwanted effects, in general, appear to differ according to age. A survey of 3,328 patients receiving 100 - 3,000 mg/day for periods up to 4 years produced an average probability of 1.85% for all side-effects. In a series of 251 children, less than 16 years old, this overall average increased to 4.47% (Noronha and Bevan 1975).

SECTION 2:

PHOTOSENSITIVE EPILEPSY AND ITS TREATMENT WITH SODIUM VALPROATE

5. PROGNOSIS OF PHOTOSENSITIVITY

5.1. Reliability of the Photosensitivity Range and its Limits.

The photosensitivity range and its upper and lower limits, although not of apparent clinical significance, are important in the diagnosis and monitoring of therapy in photosensitive epilepsy (Jeavons and Harding 1975). The most effective flash frequencies in evoking spike and wave discharge are 10-20 f.p.s. (see Section 1.8.). However, not all authors have tested every available flash rate and inter-individual variabilities above and below these frequencies are not always reported. Intra-individual variability may also exist within and between recording sessions months or even days apart (Marshall et al.1953; Herrlin 1954; Hishikawa et al.1967). Non-standardised conditions and differences in technique probably contribute to these findings but, even under constant experimental conditions, Meier-Ewert and Broughton (1967) found inconsistencies in the PMR and PCR within subjects. It is notable that these authors used the highest intensity light in a dark room which would not allow observation of the patient's face. Jeavons and Harding (1975) found that when patients were instructed to view the centre of the lamp during IPS and their direction of gaze was carefully monitored, inconsistency of responses was reduced from an incidence of 11.5% to 4.6%. Fatigue, sleep deprivation, emotional factors, alcohol, and general infection have all been found to influence PCR expression (Gerken and Doose 1969).

Others have reported a stability in the photosensitive propensity. Ulett and Johnson (1958) found between repeat EEGs a high correlation in the 'activation pattern'

for non-photosensitive individuals and those with paroxysmal responses. Pantelakis et al. (1962) observed essentially the same findings in five photosensitive epileptics several months after their initial EEGs..

It is important, therefore, particularly when treating photosensitive epilepsy, to establish whether the limits of the patient's specific sensitivity range are a reliable measure of the extent of photosensitivity so that the actual range of critical flash rates may accurately define the patient's photosensitive predisposition.

A sample was obtained of 167 photosensitive epileptics from hospitals in the Birmingham area, all of whom had received two or more repeat EEGs within 12 years.. Fig. 5.1. shows the distribution of flash rates for the lower and upper limits of the sensitivity ranges from the EEGs of these patients. The lower limit has a reasonably unimodal distribution with a peak at 8 f.p.s.. When single observations were plotted for the upper limit, no pattern of distribution was evident. However, when the data was scored in groups of 5 f.p.s., an approximately bi-modal distribution occurred with modal groups at 16-20 f.p.s. and 46-50 f.p.s.thus showing a dichotomy between a narrow and wide range. This supports the findings of Jeavons and Harding (1975) who,for clinical investigation,classified a narrow range as up to 34 flash frequencies and a wide range above 34 flash frequencies. From Fig.5.1. the turning point in the upper limit can be seen to occur between 35 - 40 f.p.s..

A reliability study of the sensitivity range limits was therefore carried out on 70 of the 167 photosensitive patients who underwent a repeat EEG within 3 months, under

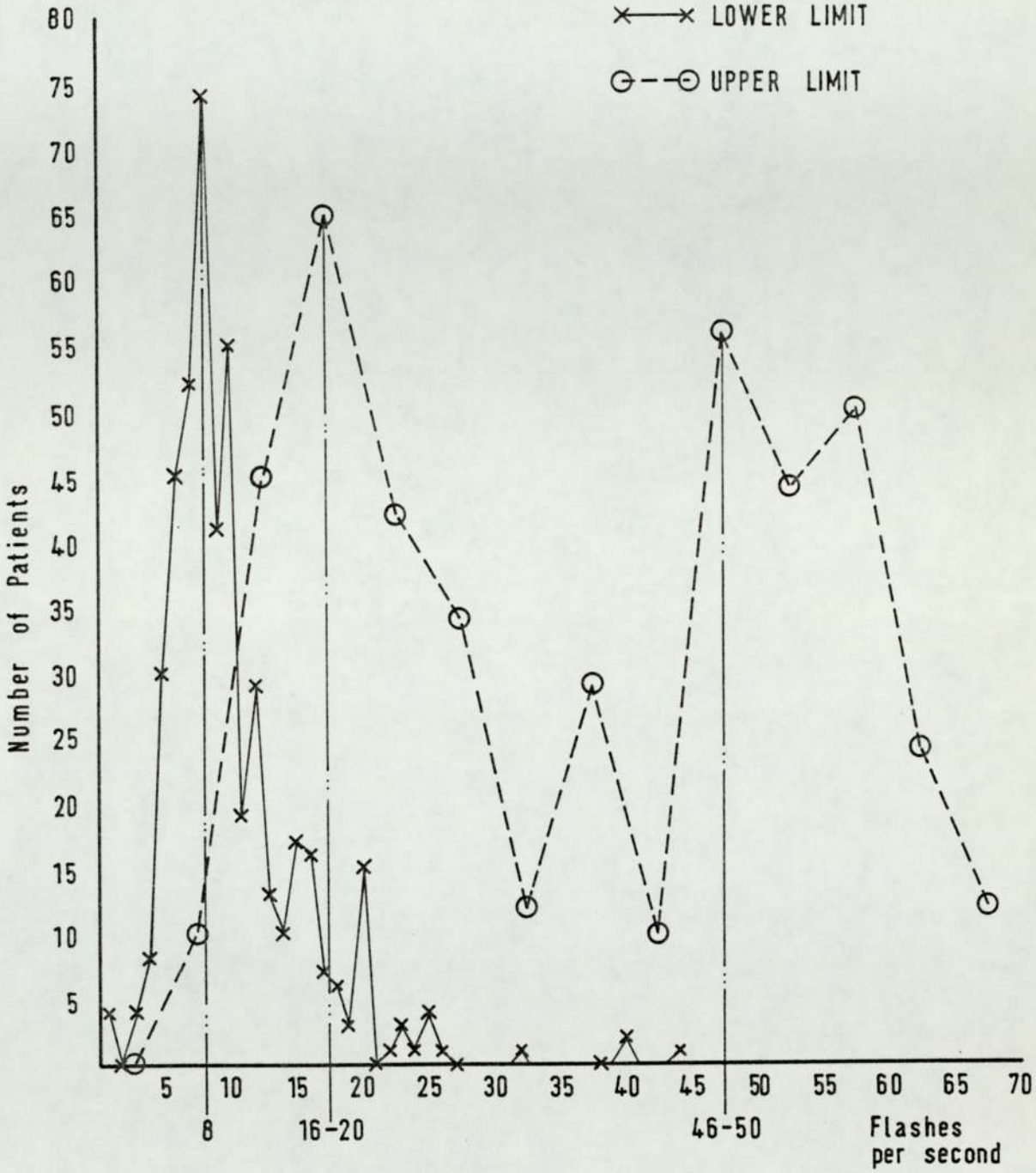


Fig. 5.1. Distribution of the Sensitivity Range Limits for the repeat E E G's of 167 patients.

standardised IPS conditions. There were 50 females and 20 males ranging in age from 5 to 40 years, mean 13 years 5 months (standard deviation, S.D., 4 years 4 months).

For each patient the lower limit and upper limit of the eyes-open sensitivity range on the second EEG were compared to those obtained at the initial recording. Fig. 5.2. shows the distribution of improvement and deterioration in both limits within the 3-month period. Improvement in the lower limit and deterioration in the upper limit are expressed as a positive deviation representing a movement to a faster flash rate. Conversely, deterioriation in the lower limit and improvement in the upper limit are shown by a negative deviation due to a lowering of the flash rate. No alteration in either limit is scored as a zero deviation. At the lower limit the mean improvement was 3.05 (S.D. 2.92) f.p.s. and mean deterioration 3.30 (S.D. 3.48) f.p.s. which showed no significant difference by an independent t test ($t = -0.34$, df55) at the 5% probability level ($P > 0.05$). Similarly, no significant difference was found between the degree of improvement, mean 8.32 (S.D. 7.72) f.p.s. and deterioration, mean 11.79 (S.D. 10.02)f.p.s. for the upper limit ($t = -1.46$ df 50, $P > 0.05$).

The number of patients showing improvement in the lower limit and upper limit were 34 and 19 respectively. Deterioration of the lower limit occurred in 23 patients and in 33 patients at the upper limit. No change in the lower limit was found in 13 patients and 6 had the same upper limit at the second recording.

No significant difference was found between the frequency of improvement or deterioration in the lower limit ($\chi^2 = 2.12$ df 1, $P > 0.05$). However, significantly more

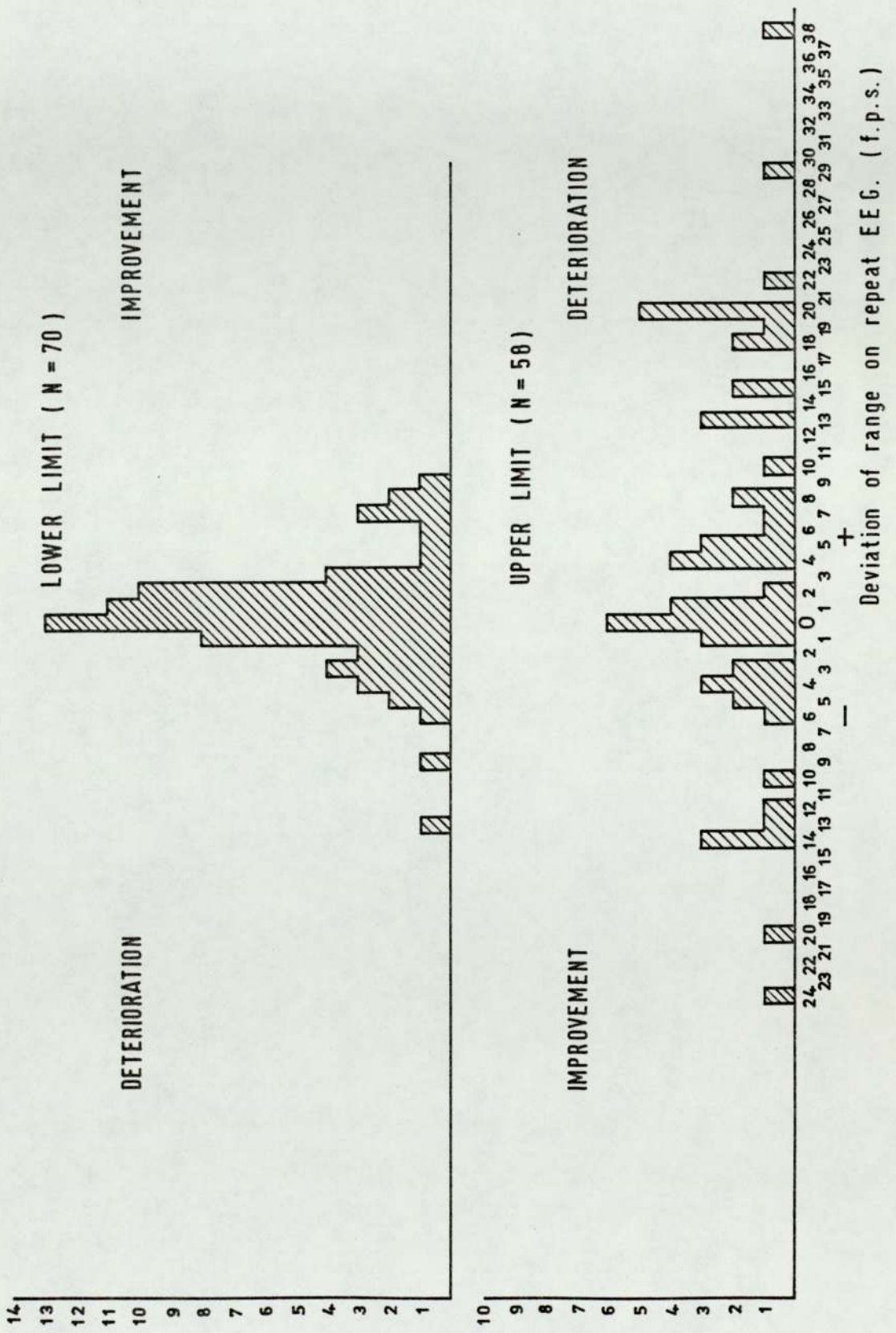


Fig. 5.2. Distribution of Improvement and Deterioration in the eyes-open Photosensitivity Range Limits within a 3-month period. (age range 5 - 40 years)

patients had a higher upper limit after 3 months (χ^2 = 3.77 df1, P = 0.05) and this was reflected in the greater number of patients exhibiting an increased rather than reduced sensitivity range (χ^2 = 5.78, df1, P = 0.01). The reasons for this are unclear but may be due to better co-operation and relaxation of the patient during the repeat investigation, allowing a more detailed study. However, in the sensitivity range no significant difference was found between the extent of improvement (mean 7.42, S.D. 5.47 f.p.s.) or deterioration (mean 11.16, S.D. 9.52 f.p.s.) at the 5% probability level (t = -1.57, df = 54).

It was previously considered that the lower limit was a more reliable index of photosensitivity than the upper limit, possibly due to the tendency of photostimulators to produce subharmonic flashes when set at high flash rates (Jeavons, Herrick, Maheshwari and Harding, 1975). The overall deviation in the lower and upper limits of the 70 patients (Fig.5.3.) apparently suggests that the lower limit (mean 2.57, S.D. 2.70 f.p.s.) follows a roughly normal distribution while that of the upper limit (mean 9.43, S.D. 7.92 f.p.s.) is far more variable. However, as the flash rate increases, so the interstimulus interval becomes reduced, producing a much finer distinction between flash rates. For example, a change from 10 to 11 f.p.s. is a change of approximately 10% or an interstimulus interval of 9.1 msec. A change from 50 to 55 f.p.s. is also a change of 10% but of only 1.8 msec. interstimulus interval (Harding, Herrick and Jeavons - in press). When percentage deviation is considered (Fig. 5.4.) the distribution of alteration in flash rate for both limits follows a very similar pattern.

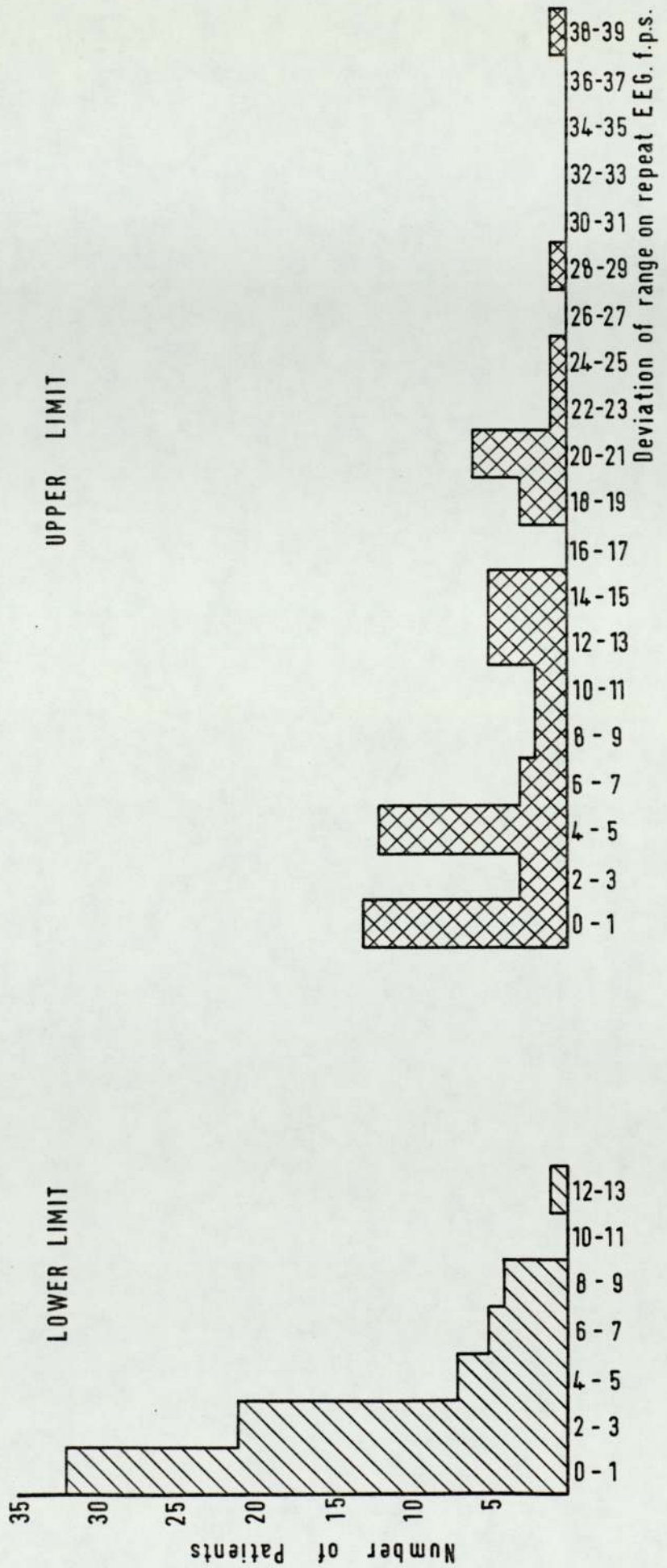


Fig. 5.3. Deviation in the eyes-open Photosensitivity Range Limits for a sample of 70 patients within 3 months (age range 5 – 40 years)

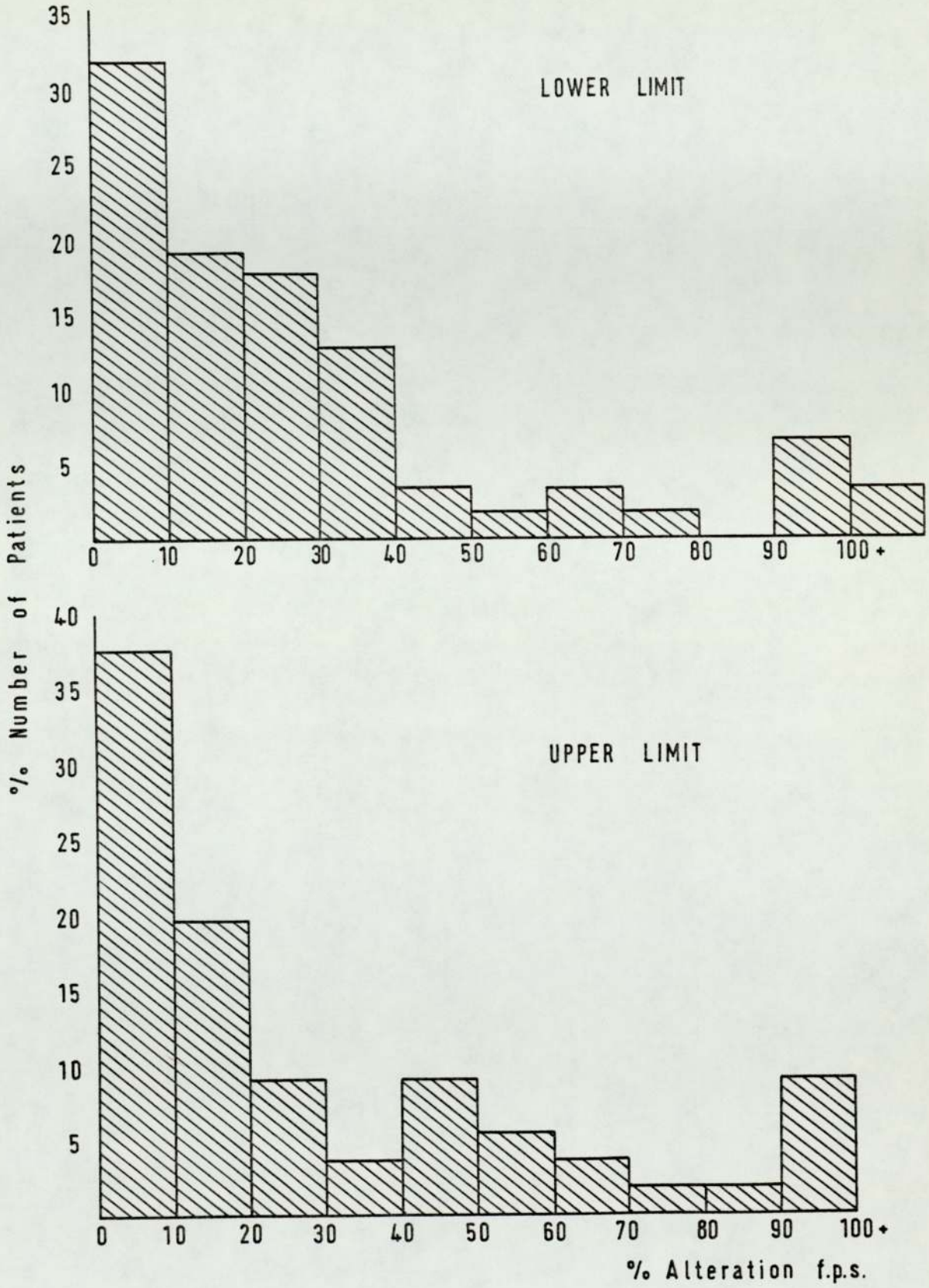


Fig. 5.4. Percentage Alteration in Lower and Upper Sensitivity Range Limits within 3 months.

Therefore, within a 3-month period between EEGs both limits showed close repeatability, and it can be concluded that the lower and upper limit of the sensitivity range provide a reliable measure of the photoconvulsive tendency.

Of the 70 patients tested, 34 had been receiving various types of anticonvulsants, other than sodium valproate, during the study. Twenty-seven were taking the same medication and another 7 underwent either a complete change in medication or an addition or subtraction of another drug. To determine whether medication affected photosensitivity the 'stable treatment', 'changed treatment' and 'no treatment' groups were investigated separately. Comparisons made between the groups for the number of patients improving or deteriorating at the lower limit showed no significant differences ($P > 0.05$). As regards the upper limit, after 3 months more patients were seen to deteriorate on 'stable treatment' than in the 'no treatment' group ($\chi^2 = 3.64$, df1, $P = 0.05$). It has previously been mentioned that overall more patients' upper limits followed this trend. However, comparison of both these treatment sub-groups with the 'changed treatment' patients, using the Fisher exact probability test , gave non-significant results at $P = 0.25$ and $P = 0.35$ between 'stable treatment' and 'no treatment' groups respectively. When considering the degree of improvement and deterioration between all groups, no significant difference was found for either the lower or upper limit (independent t tests, $P > 0.05$).

In conclusion, therefore, none of the medication being received had any beneficial effect on the photosensitivity range.

Period of Follow-up	Lower Limit						Upper Limit						Sensitivity Range					
	Imp.		Det.		Dev^{n}.		Imp.		Det.		Dev^{n}.		Imp.		Det.		Dev^{n}.	
	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.	$\bar{x}$	SD.
≤ 3 mths	3·05	2·92	3·30	3·48	2·57	2·70	8·32	7·72	11·79	10·02	9·43	7·92	7·42	5·47	11·16	9·52	9·53	8·55
1/0 yrs	2·94	2·48	2·10	1·66														
2/0 yrs	3·50	3·77	2·90	4·07														
3/0 yrs	4·60	5·38	3·10	4·11														
4/0 yrs	5·20	6·38	2·20	3·12														
5/0 yrs	4·31	3·34	3	4·27														
6/0 yrs	5·20	4·67	3	3·58														
7–12 yrs	5·25	5·91	4·67	2·53														

Table 5.1. Reliability and Prognosis : Means and Standard Deviations for the Sensitivity Range and its Limits.

(Improvement, Imp.; Deterioration, Det.;
Overall Deviation, Dev^{n}.; Mean, $\bar{x}$;
Standard Deviation, SD.)

'Treatment'	Improvement		Deterioration		No Change	
	LL	UL	LL	UL	LL	UL
'Stable'	10	4	8	18	9	1
'Changed'	3	2	3	3	1	2
'None'	18	11	12	11	3	3

Table 5.2. Number of Reliability patients in each treatment sub-group (Lower Limit, LL; Upper Limit, UL)

5.2. Prognosis.

Although several authors have commented on the high incidence of photoconvulsive epilepsy between 5 - 15 years, all agree that photosensitivity tends to fade with increasing age (Herrlin 1954; Charlton and Hoefer 1964; Capron 1966; Troupin 1966). A PCR is rare before the age of 6 years (Doose et al. 1969b) and even though the onset of photosensitivity has been reported between 2 - 58 years (Jeavons and Harding 1975), 76% of all cases showed PCR penetrance between 8 - 19 years, 12.6% up to 7 years and only 11.7% after 20 years of age. The modal age of onset was 12 years. It appears evident that puberty greatly influences the genesis of photosensitivity and that the condition is probably associated with gene-controlled hyperexcitability (Doose et al. 1969a, b; Scollo-Lavizzari 1971). Whereas 26.2% of siblings, aged 6-15 years old, of photo-

sensitive epileptics were found to have a PCR, less than 8% of parents had positive findings (Doose et al. 1969a). Mothers of photosensitive children may sometimes remark on being disturbed by flicker or patterns when younger, but they rarely show abnormal EEGs (Jeavons 1972b). In one family of 11 children, 3 of whom had a clinical history of photosensitive epilepsy, 3 younger, fit-free female siblings were found to have latent spike and wave PCRs.. Occipital abnormalities were seen in 5 siblings and the mother, now aged 48, had occipital spike and wave abnormality during IPS (Herrick 1973). In the same study one woman (39 years) with a previous history of epilepsy, now only showed occipital spikes at low flash rates. Her daughters, however, aged 22 and 13 years, both had PCRs and were photosensitive epileptics.

The eventual abatement of photosensitivity is therefore generally accepted. However, prognosis is better when associated with 'functional disorders' rather than organic conditions, viz. degenerative brain processes, widespread vasculopathies (Lopez 1973). Even so, a patient may continue to be at risk for at least 8 years after onset of their photosensitivity. Patients can be classified according to the severity of their condition (Bickford et al. 1953; Jeavons and Harding 1975) and may shift from one group to another. Therefore, besides any eventual improvement, it is possible for patients to deteriorate first, e.g. spontaneous fits only and laboratory sensitivity to the addition of seizures caused by environmental flicker such as the television, or sunlight.

5.2.1. Developments over 12 years.

Over a period of 12 years the 167 photosensitive patients received a series of repeat EEGs at approximately yearly intervals. Throughout the study the minimum age was 5 years and maximum 40 years, mean 13 years 5 months (S.D. 4 years, 11 months).

As far as possible, laboratory conditions were standardised but techniques developed and obviously over such a long period equipment was replaced by new recording instruments, usually of a higher technical standard. Due to the tendency of old photostimulators to produce aberrations at high flash rates, the lower limit was selected for study, due to its easy identification and greater consistency in the earlier EEG records. Fig. 5.5. shows the mean alteration and standard deviation for improvement and deterioration in the lower limit of the sensitivity range at each year of follow-up over the 12-year period. As with the reliability study, improvement refers to an increase in the lower limit, so that a faster flash rate is required before a PCR can be evoked. Deterioration corresponds to a reduction in flash rate. The graph shows that, although the mean improvement tends to be somewhat larger than mean deterioration, there is wide variation as seen by the overlap of standard deviations. The mean variation of either trend never exceeds 5·25 f.p.s., which is nearly twice the variation seen within only a 3-month interval.

Obviously, over 12 years the patient group became mobile with movement to and from the area. Therefore with successive years of follow-up, the sample size decreased. However, certainly over 3 years there is very little change in

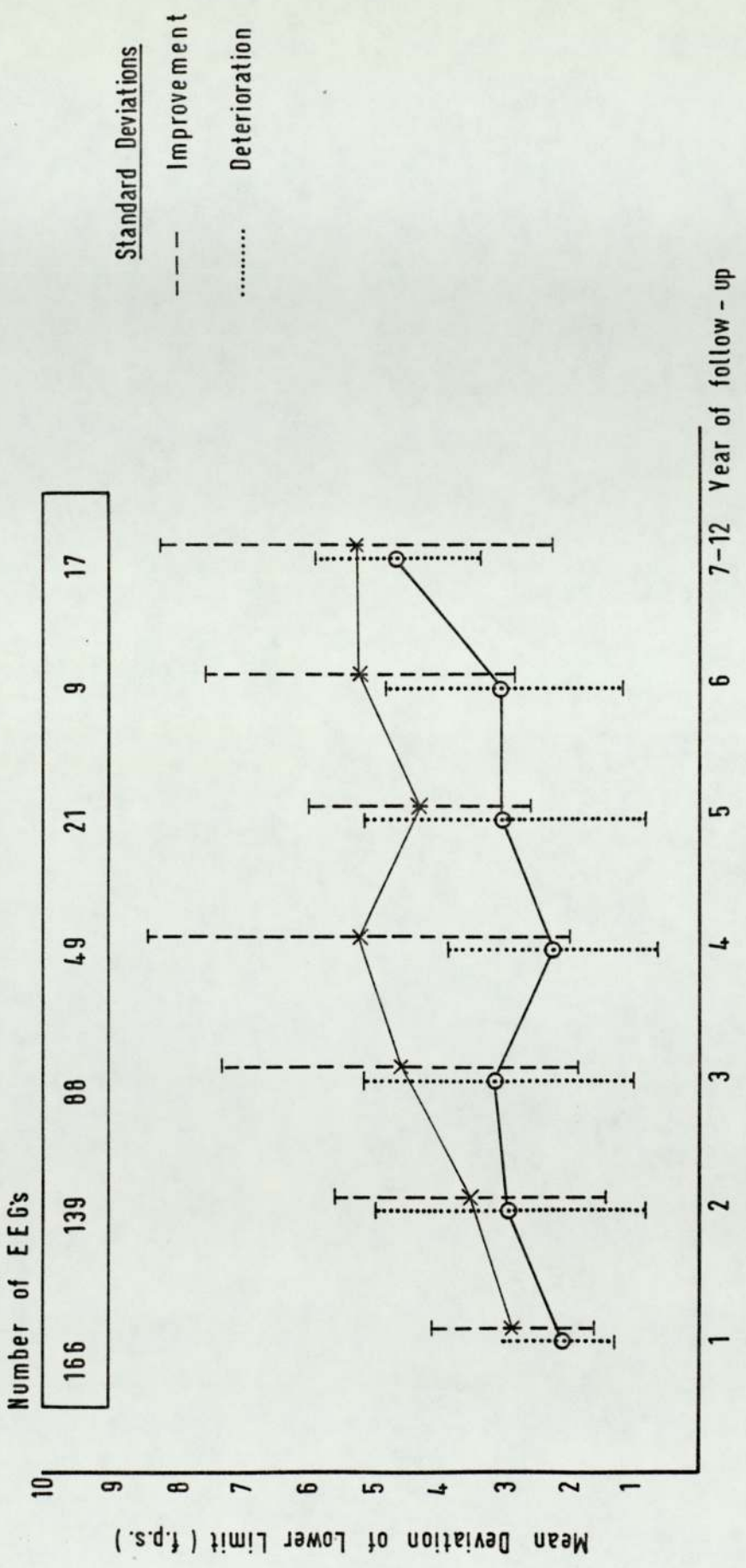


Fig. 5.5. Prognosis of the eyes-open Photosensitivity Range Lower Limit during 12 years of follow-up EEG's. (age range 5-40 years)

the lower limit of photosensitivity and, even after 7-12 years, (mean age 21 years, 8 months, S.D. 5 years 5 months), the difference between improvement and deterioration was less than 1 f.p.s. (0.58 f.p.s.). Overall, no significant trend is seen in the lower limit and it is evident that photosensitivity does not show marked spontaneous improvement over a 12 year period.

5.2.2. Clinical history.

Eighty-seven photosensitive patients who had only undergone one EEG investigatior , were compared with the 167 prognosis patients to determine whether seizure type was related to the photosensitive clinical history. The patients were grouped according to Jeavons and Harding (1975) classification (see Section 1.4). Patients in Group I are flicker-sensitive only; Group II have spontaneous fits as well as flicker-indiced seizures; Group III only have spontaneous fits but are photosensitive during laboratory IPS.

Of the 254 patients, 89 were male and 165 female (ratio 100:185); however, there is no significant difference between the proportion of males and females in each photosensitive group (χ^2 = 3.36, df2, P > 0.05). The overall mean age was 13 years 6 months (S.D.5 years 3 months). It is significant that about half the patients had a clinical history of purely flicker sensitive fits (51%) whereas 28% also had spontaneous fits and 20% only had spontaneous fits without any implication of a light precipitator (χ^2 = 39.24, df2, P = 0.001). Variation also exists within each group according to seizure type. Over all patients, 65% suffered with tonic-clonic fits, the highest incidence (41.7%) occurring in Group I. Minor absences were seen in 10.7%

of patients, in 7% of which the attacks could occur spontaneously (Groups II and III) and in 3.7% they were precipitated only by flickering light. Partial seizures with focal motor or psychomotor attacks were fairly rare, 3.7% of all patients, but two-thirds of these patients were in Group I. Myoclonic jerks rarely occurred alone (3.3%) and were only present in those patients who had spontaneous fits with or without additional photosensitive seizures. In fact myoclonic jerks were almost twice as frequent when occurring together with other forms of seizure (5.8%) and these patients constituted one-third of the mixed seizure group. Mixed seizures comprised 17.4% of all patients, the second largest group, and were particularly evident in those patients who had spontaneous seizures, with or without additional fits induced by flicker. The most common combination of seizures was tonic-clonic convulsions plus absence seizures (6.6%).

From the clinical aspect, the majority of photosensitive patients do have epileptic fits induced by flickering light in the normal environment. However, nearly one-third are also at risk from apparently spontaneous attacks, and others have spontaneous attacks only, without any clinical implication of light precipitation. The most frequent type of seizure in response to flickering light is a tonic-clonic fit. The occurrence of two or more forms of seizure is more usual in those patients either, or also with spontaneous epileptic attacks.

Photosensitive epilepsy refers to those patients with a positive diagnosis of a fit induced by flickering light or pattern in the everyday situation (Groups I and II), (Jeavons and Harding 1975). The above study indicates

therefore, that if photosensitivity could be successfully treated, about two-thirds of such patients would be rendered free from major, generalised epilepsy.

6. THE EFFECT OF SODIUM VALPROATE ON THE BASIC EEG

6.1. Patient Sample.

The most effective therapy for the photosensitive epileptic has been the avoidance of the stimulating conditions which provoked the fit (Jeavons and Harding 1975). For instance, the 'television epileptic' was instructed not to view the television at close range, approach the set nor adjust the controls and to view in a well-lit room. The covering of one eye and polarised spectacles have also been recommended by these authors for flicker-sensitive patients when confronted with hazardous situations. However, the resting EEGs of 460 patients showed spike and wave abnormalities in 54% of all cases, with little difference between the purely photosensitive epileptics, patients with spontaneous and photosensitive seizures, and those patients with only spontaneous epilepsy but laboratory photosensitivity. Anticonvulsant therapy is generally prescribed for patients with spontaneous seizures, although there has been little evidence that such treatment produces a consistent improvement in photosensitivity (see Section 3.6.). Chapter 5 supports these findings. Until recently, ethosuximide appeared to be the only exception in that it has a positive effect on 3 c.p.s. spike and wave absences induced by IPS (Jeavons et al. 1976).

In 1973, Doose and Gerken suggested the possibility of using dipropylacetate in the prophylaxis of symptom-free siblings of photosensitive epileptics. From October 1973 to January 1977, a study was therefore conducted on the effect of this drug on the basic EEG, the visual evoked potential (VEP) and the photoconvulsive response (PCR) of photo-

sensitive patients. Fifty patients were selected for treatment and were investigated before receiving the drug, during therapy and, in 16 cases, after treatment. Patients were referred from hospitals in the Birmingham area. Twenty-nine patients were investigated in detail at the Neuropsychology Unit at Aston University, where computing facilities were available. Sixteen patients were followed up at the Dudley Road Hospital and five at the Birmingham Children's Hospital. A clinical history of fits induced by flickering light only occurred in 22 patients (Group 1); 16 patients had photosensitive seizures and spontaneous attacks (Group II); 10 patients were only photosensitive during laboratory IPS and had spontaneous fits (Group III). One young female patient (7 years 4 months) was photosensitive but not epileptic. She was, however, the sister of one of the photosensitive epileptics and was being treated prophylactically for her abnormal basic EEG and photosensitivity. Another patient (18 years 11 months) was also photosensitive but only had a history of syncopal attacks without any direct evidence of light precipitation . She did, however, report peculiar sensations when approaching too close to the television.

At the beginning of the study, patients' ages ranged from 6 years 2 months to 25 years 6 months (mean 14 years 9 months, S.D. 4 years 10 months). There were 31 females and 19 males (ratio 163:100).

6.2. Treatment Regime.

Dipropylacetate was administered as its sodium salt, sodium valproate (Epilim (R)) in 200 mgm. tablets. All patients received at least one pre-drug EEG, and in some cases two investigations. (In all figures, the last pre-drug EEG is referred to as Pre-Epilim 2 or P2). Thirty-three patients had been taking anticonvulsants before sodium valproate treatment. In four cases these drugs were stopped before the last pre-drug EEG. Of the 29 patients, medication was as follows :-

Drug	Number of Patients
Phenobarbitone	18
Phenytoin	13
Ethosuximide	8
Sulthiame	3
Acetazolamide	1
Amitriptilline	1
Sodium Amytal	1
Carbamazepine	1
Diazepam	1
Ethotoin	1
Imipramine	1
Pheneturide	1

Fourteen patients were taking only one drug, 9 patients two drugs, and 6 patients three or more anticonvulsants. As sodium valproate was introduced, anticonvulsants were withdrawn in 18 patients gradually, so as to avoid status epilepticus. Eleven patients continued to take reduced dosages of their previous medication throughout sodium valproate treatment. Of these, 5 patients remained

on ethosuximide, 4 patients on phenobarbitone, 3 on phenytoin and one patient still received acetazolamide. One patient with enuresis took 10 mgm. of imipramine each night. Overall 8 patients only received one extra drug in addition to sodium valproate. Twentyone patients were not taking any other medication one month before or during treatment.

Sodium valproate was usually administered as an initial dose of up to 800 mg/day depending on the age of the patient. However, 13 patients began treatment with 1000 mgm. and one other patient started with 1200 mgm. daily (although this was reduced to 1000 mgm. two months later). Introduction of the initial dosage was gradual, over at least 9 days, e.g.

200 mgm. twice a day for 3 days,

200 mgm. three times a day for 3 days,

400 mgm. twice a day for 3 days or subsequently.

The first follow-up EEG was done one month after the patient had reached his or her full initial dosage. Subsequently, repeat EEGs were taken at one or three month intervals, depending on whether further increase in dosage was required. Sodium valproate was always given in two or three divided doses and patients were advised to take the tablets with a drink of milk or plenty of water, but preferably after a meal. Some young patients took their mid-day dose during the afternoon, after school. This ensured that these patients received their full dosage.

6.3. Basic EEG Recording Technique.

Although laboratory studies were carried out in three departments, the methods of investigation were essentially similar. As mentioned previously, computer facilities were only available at the Neuropsychology Unit, where the tape recording of the basic EEG and evoked potentials were carried out. EEG recording was made on either a 16-channel Elema Schönander or a 12-channel S.L.E. machine. Scalp silver-silver chloride disc electrodes were placed according to the international 10/20 system (Jasper 1958).

During each investigation, the patient lay in a supine position in a well lit room and was encouraged to relax and co-operate with instructions. Before sodium valproate treatment, a full routine EEG was taken for at least one pre-drug investigation. Several montages were used including parasaggital, bi-temporal and a transverse montage. Hyperventilation was performed by the patient with eyes-open and eyes-closed for 3 minutes. Follow-up EEGs during treatment were conducted using the parasaggital montage. Normal recording was made with a paper speed of 30 cm/sec., an overall time constant of 0.3 sec., and a 100 μv/cm. gain. High frequency filters were used only when absolutely necessary, so that high frequency spike abnormalities would not go undetected.

6.4. Interpretation of the Basic Record.

6.4.1. Abnormalities.

EEGs were classified as abnormal only if bilateral or localised discharges of spike and wave or spikes were present. Non-specific abnormality described the occurrence of slow waves or doubtful non-localised sharp waves. Prior to sodium valproate treatment, 31 of the 50 photosensitive patients (62%) had spontaneous abnormality in their basic EEGs. Five other patients (10%) exhibited non-specific abnormality and 14 patients (28%) had normal records. Significantly more patients had abnormal EEGs before commencement of sodium valproate (χ^2 = 6.42 df1, P = 0.01).

Fig. 6.1. and Table 6.1. show the effect of sodium valproate on the spontaneous EEG, expressed as the percentage of abnormal records at various stages of the treatment. Spike and spike and wave abnormalities were considerably reduced by 1000 mg/day. However, withdrawal of sodium valproate increased the frequency of abnormal EEGs to a a similar level as seen in the pre-drug records.

Throughout the drug trial, patients were at varying dosages of sodium valproate and several EEG investigations usually occurred within the duration of a particular dosage. The EEG showing the most favourable response in photosensitivity at each dose level, at the earliest time interval since commencement of treatment, was normally selected for analysis. A patient's optimum dosage refers to that EEG showing an individual's maximum improvement during their duration of treatment. The time interval from the last pre-drug EEG to the optimum dosage recording was 1 month to 2 years 9 months (mean 9.34 months, S.D. 8.07 months). The average age of patients at this stage of treatment was 15 years 6 months (S.D. 4 years 10 months). At optimum dosage only 12 patients now

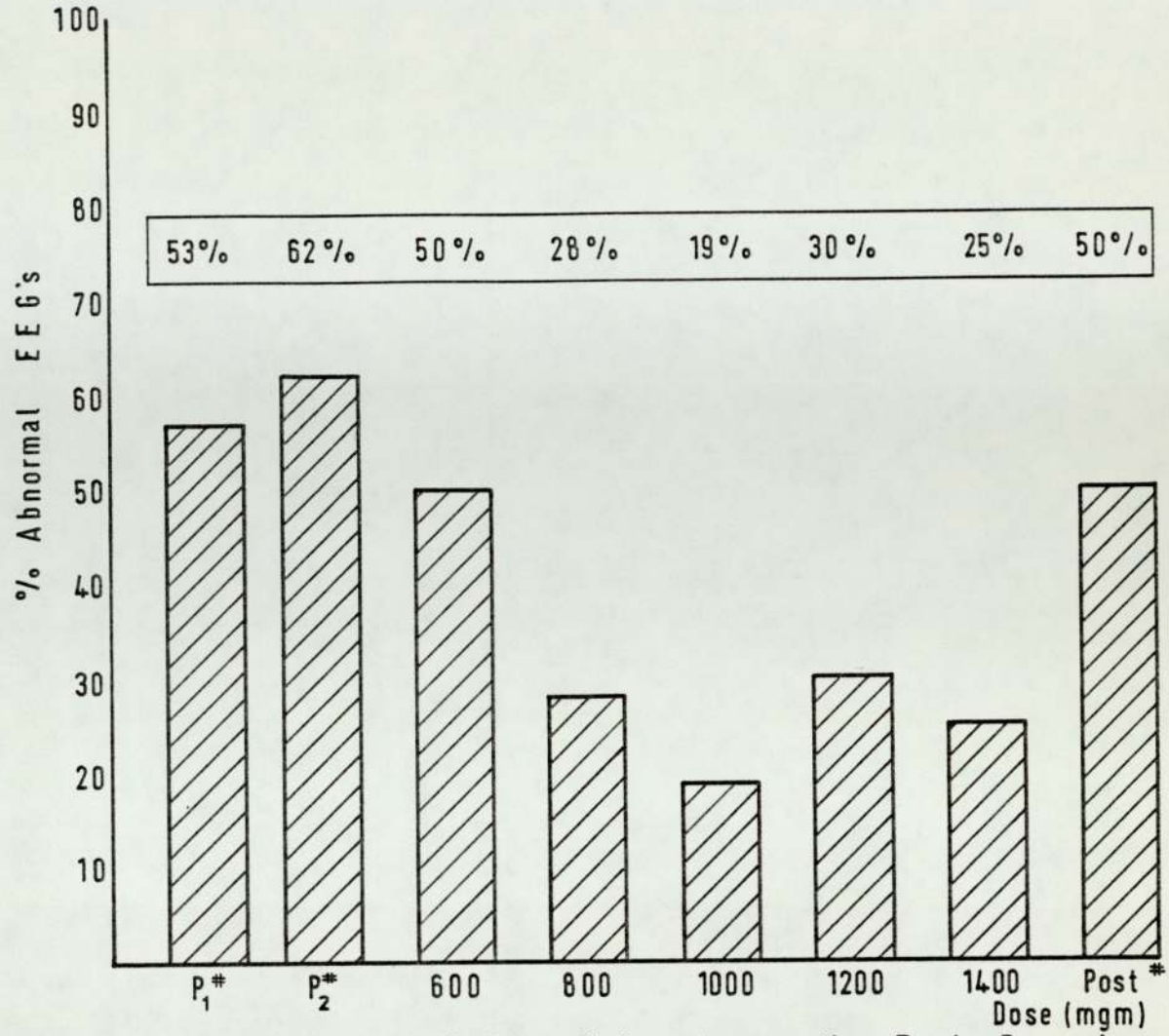


Fig. 6.1. The effect of Sodium Valproate on the Basic Record

Dose	Abnormal	Non-Specific Abnormality	Normal	Total
$P_1^{\#}$	17 (57%)	3 (10%)	10 (33%)	30
$P_2^{\#}$	31 (62%)	5 (10%)	14 (28%)	50
600	2 (50%)	1 (25%)	1 (25%)	4
800	8 (28%)	7 (24%)	14 (48%)	29
1000	7 (19%)	0	30 (81%)	37
1200	6 (30%)	2 (10%)	12 (60%)	20
1400	1 (25%)	1 (25%)	2 (50%)	4
Post#	9 (50%)	2 (11%)	7 (39%)	18

Table 6.1. Distribution of the Basic EEG Record at dose levels of Sodium Valproate.

(P_1 / P_2 = 1st/2nd Pre-Epilim record; Post = Post-Epilim record)

had clearly abnormal EEGs and in 35 patients the spontaneous EEG was normal. This difference was highly significant (χ^2 = 11.26 df1, P = 0.0005).

Of the 31 patients who previously had spontaneous spike and wave discharges in their pre-drug EEGs, 17 became normalised at optimum dosage, the spike and wave became reduced to non-specific abnormality in 3 patients and 11 retained abnormal EEGs. All 5 patients initially with non-specific abnormality now showed no spontaneous aberrant activity. The frequency of EEG normalisation at optimum dosage was significantly greater than retention of abnormality (χ^2 = 3.67 df 1, P = 0.05). Eleven of the 22 normalised patients received further follow-up investigations after the optimum dosage EEG and at the same dose of sodium valproate. Only 2 patients relapsed from a normal EEG to the addition of non-specific abnormality. The incidence of stabilised EEGs was significantly higher (χ^2 = 4.46 df1, P = 0.025).

6.4.1.1. Interaction between the basic record and photosensitivity

Thirty-nine of the 50 photosensitive patients achieved either a significant improvement or total abolition of photosensitivity (see Section 7.4.). At this level dosage ranged from 600 - 1600 mg/day with a modal dosage of 1000 mgm. (N = 20) and a mean of 1035.90 (S.D. 180.44) mg/day. The modal dosage for basic EEG normalisation throughout the study was also 1000 mgm. (N = 11) but with a slightly lower mean of 933.33 (S.D. 149.07) mg/day. It was noted that in many patients sodium valproate appeared to have a differential effect on spontaneous and photically evoked abnormalities.

During treatment, 26 of the 36 patients with spike and wave or non-specific abnormality in their pre-drug EEGs

achieved a significant improvement in photosensitivity. Basic record normalisation had, however, already occurred in 9 of the 26 patients; 7 showed significant improvement in both the resting and photically activated EEG at the same follow-up investigation, but 8 other patients, although less sensitive to photic stimulation, still retained basic EEG abnormalities. The EEGs of the remaining two patients became normalised after they had reached a significant reduction in photosensitivity. The other 10 patients of the 36 pre-drug, abnormal EEG patients did not show a marked improvement in photosensitivity during sodium valproate treatment, but in 6 of these cases the resting records had become normalised.

Comparison was made to determine whether any differential effects of sodium valproate existed between spontaneous and photically evoked EEG abnormalities. Obviously exact comparison was related to the frequency of the follow-up EEGs. It was therefore possible that the 7 patients, who showed marked improvement in both conditions at the same investigation, may have actually undergone a separate improvement of basic EEG abnormalities and the PCR but this went undetected due to the overlapping time interval between EEGs. No significant difference was found between patients achieving a marked improvement in photosensitivity and those who did not as regards the likelihood of basic EEG normalisation (χ^2 = 0.02 df1, P > 0.05). However, significantly more patients acquired normality of the spontaneous EEG before or concurrently with a real improvement in photosensitivity (χ^2 = 4.5 df1, P = 0.025).

Therefore,of the 36 previously abnormal patients, 18 acquired EEG normalisation and a significant reduction in the photosensitivity range. In this group the time period taken for spontaneous EEG improvement ranged from 1 month to 2 years 4 months (mean 7.88 months, S.D. 8.17 months), and for improvement in photosensitivity 1 month to 2 years 9 months (mean 12.35 months, S.D. 9.37 months). Normalisation of the spontaneous EEG occurred significantly earlier in these patients than improvement to IPS ($t = -2.03$ df17, $P = 0.05$).

Comparison was also made within these 18 patients between the dosage required for basic EEG normalisation (mean 911.11, S.D. 152.35 mg/day) and that for significant improvement of photosensitivity, (mean 977.78, S.D. 161.78 mg/day). Beneficial effects on the basic EEG occurred at a significantly lower dosage of sodium valproate ($t = -2.38$ df 17, $P = 0.025$).

6.4.1.2. Withdrawal of sodium valproate.

Of the 16 patients eventually withdrawn from sodium valproate treatment, 8 had spike or spike and wave discharge in their basic EEGs prior to treatment and in 2 other patients the EEGs contained non-specific slow waves and/or sharp waves. Normal basic EEGs occurred in 6 patients. No significant difference existed between the frequency of normality or some degree of EEG abnormality before therapy (Binomial test, $P = 0.227$). However, at optimum dosage this difference proved to be significant at $P = 0.038$. After a mean treatment period of 8.4 months (S.D. 6.84 months) 12 patients had normal EEGs, spike and wave abnormality remained in 3 patients and one other patient's EEG now only contained non-specific abnormality during hyperventilation. After

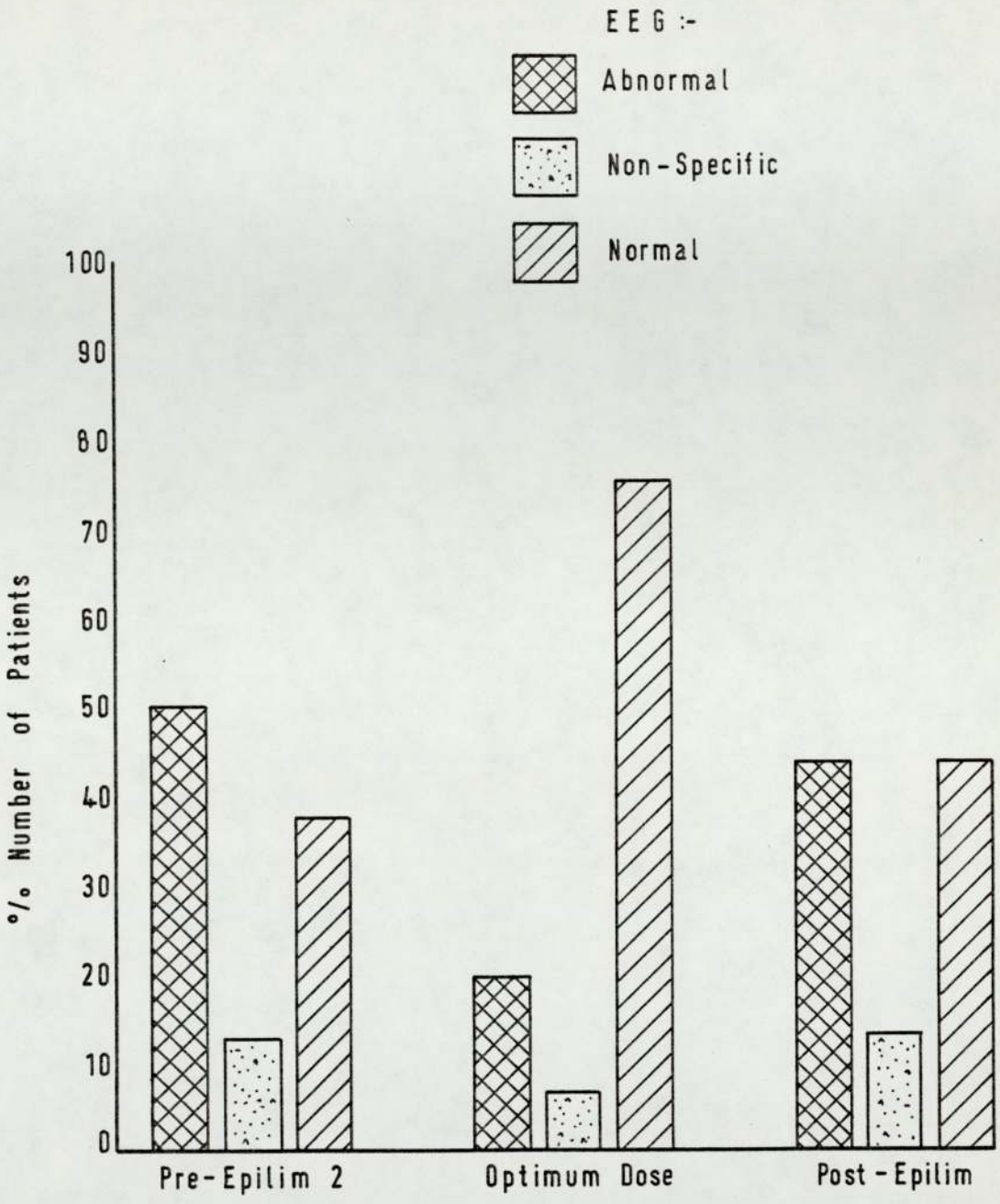


Fig. 6.2. Condition of the Basic EEG Record before Sodium Valproate, at Optimum Dosage, and after withdrawal of Sodium Valproate. (Number of patients = 16)

withdrawal of sodium valproate over 1-7 months (mean 3.12 months, S.D. 2.04 months) the difference between the incidence of abnormal EEGs (N = 7), non-specific abnormalities (N = 2) and normal basic records (N = 7) was again non-significant (Binomial test P = 0.402).

6.4.1.3. Dosage effects on structural changes in abnormality.

Throughout the study, the basic records of 29 patients attending the Neuropsychology Unit were analysed in detail, at the various dose levels, to determine whether sodium valproate affected structural changes in spontaneous EEG abnormality prior to its total disappearance. Detailed analysis of the pre-drug record was possible on 24 patients. Of these, 12 (50%) had definite abnormalities, 3 (12.5%) exhibited non-specific abnormality and the remaining 9 (37.5%) patients had normal EEGs. More than one form of spontaneous abnormality was seen in 9 patients. Generalised abnormality alone occurred in 7 patients, localised abnormality in 1 patient and both forms were simultaneously seen in the EEGs of 7 patients. Six patients (25%) exhibited abnormalities clearly associated with eye-closure.

Generalised atypical spike and wave (N = 7, 29.2%) and polyspike and wave complexes (N = 7) were the most common abnormalities. Generalised slow waves occurred in 5 patients (20.8%). The most frequent localised abnormalities were spikes (N = 6, 25%) or sharp waves (N = 6). In two patients spikes or sharp waves occurred in the rolandic region and in 4 patients were confined occipitally. Three patients possessed localised degraded atypical spike and wave in the posterior derivations and in one other patient similar activity was seen anteriorly.

EEGs were examined at successive doses of sodium valproate. At 800 mg/day, 8 out of 16 patients(50%) had completely normal EEGs. Definite abnormality was seen in 5 patients (31.25%) and non-specific discharge in 3 cases (18.75%). Atypical spike and wave, and polyspike and wave complexes were again the most usual aberrations but only occurred in 3 patients respectively. Isolated posterior sharp waves were exhibited in 4 patients (25%). Two or more forms of spontaneous abnormality occurred in 5 patients and discharge associated with eye-closure was present in 3 cases.

Detailed EEG analysis at 1000 mgm. was available on 24 patients. Seventeen patients (70.8%) now had normal basic EEGs. Five patients (20.8%) still retained spike and wave abnormalities and 2 patients (8.3%) only non-specific paroxysms. Atypical spike and wave or generalised slow waves occurred in 3 patients (12.5%) respectively. Typical generalised spike and wave, generalised spikes and polyspike and wave were each seen in 2 patients. Two patients had rolandic spikes and 2 other cases, occipital spikes. Several types of discharge occurred in 5 patients, and in 2 cases abnormality appeared immediately after eye-closure.

Nine out of 13 patients (69.2%) had normal EEGs at 1200 mg/day. EEGs were abnormal in 3 cases (23.1%) and contained only non-specific slow waves in 1 patient (7.7%). Three patients had generalised abnormality only and purely localised discharge was seen in another patient. No patients had typical spike and wave, 2 patients (15.4%) had retained generalised atypical spike and wave, 1 patient polyspike and wave, and 1 patient generalised polyspikes. This latter person's EEG also contained isolated posterior spikes

and sharp waves. In only one person were abnormalities associated with eye-closure.

Of the 16 patients eventually withdrawn from sodium valproate treatment, 14 had detailed analysis of the spontaneous EEG. Prior to withdrawal the frequency of normal basic records was 66.7% at the last-treatment investigation which decreased to 35.7% (N = 5) after drug withdrawal. Abnormal EEGs were seen in 7 patients (50%) and non-specific abnormalities in 2 cases (14.3%). The overall picture was very similar to that seen before the therapy. Seven patients had more than one type of abnormality. Eye-closure induced discharge occurred in 3 patients (21.4%). Atypical spike and wave was the most frequent generalised paroxysm, occurring in 4 patients (28.6%) followed by polyspike and slow waves (N = 3), and generalised slow waves (N = 2, 14.3%). Four patients had isolated sharp waves predominantly in the posterior derivations and also, in 1 patient, occurring in the rolandic area. Localised atypical spike and wave, occipital spikes, or occipito-parietal sharp waves and slow waves were seen in 2 patients respectively.

A series of parametric, correlated t tests were used to compare the maximum duration and maximum amplitude of spontaneous EEG abnormality at each dose level of sodium valproate with the findings obtained at the last pre-drug EEG (see Table 6.2.). At 800 mg/day one patient also received phenytoin which was further reduced at 1000 mgm. At this dosage another patient continued with reduced phenobarbitone. No patients were taking additional anticonvulsants at 1200 mgm. Comparisons at 1400 mgm. and 1600 mgm. daily were invalid, due to the exceptionally small number at each dosage.

EEG	Duration (secs.)		Amplitude (μv.)	
	Mean	S.D.	Mean	S.D.
Pre-Drug	2·71	1·96	284·0	57·44
800 mgm	1·22	1·10	184·0	118·7
1000 mgm	1·46	2·21	127·73	138·68
1200 mgm	0·48	1·25	45·56	90·57
Post-Drug	0·92	1·03	199·00	109·20

Table 6.2. Structural changes in spontaneous EEG abnormalities at varying dose levels of Sodium Valproate.

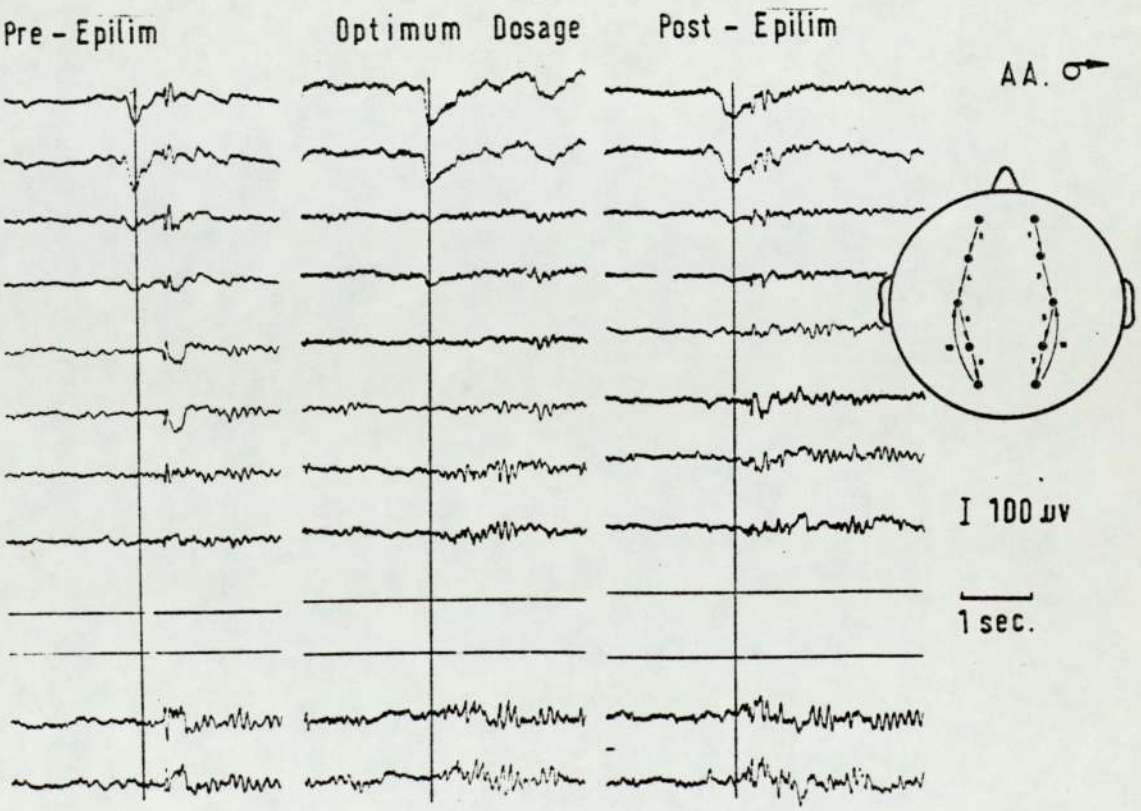


Fig. 6.3. Spike and slow wave spontaneous EEG abnormality evoked by Eye-closure disappears at 1000 mg/day of Sodium Valproate but returns after 2 months of drug withdrawal.

At 800, 1000 and 1200 mgm. daily of sodium valproate, spontaneous EEG abnormalities overall had significantly reduced in persistency and magnitude ($P \leq 0.0005$). However, after only an average withdrawal period of 2.77 months (S.D. 1.76 months), the degree of abnormality in the basic record was not significantly different from that seen before treatment. Similar results were obtained when the patients on additional medication were excluded from analysis.

6.4.1.4. Conclusions.

Sodium valproate is efficacious in removing spontaneous EEG abnormalities. Even at a low dosage of 800 mgm. alone, significant improvement was seen in the persistency and amplitude of the abnormality. By optimum dosage the EEGs of 61% of patients previously characterised by spike, spike and wave, slow waves or sharp waves were completely normalised with a high stability of this improvement during continued treatment. It was also significant that many patients acquired basic EEG normality on average 4.5 months before any appreciable reduction in the photoconvulsive propensity. Also, as patients tended to undergo gradual dosage increases during this study, it became evident that basic EEG transformation would consistently occur at a lower dosage of sodium valproate than the optimum dosage required for a significant improvement in photosensitivity. Overall, two-thirds of patients with some form of spontaneous EEG abnormality prior to sodium valproate therapy became normalised at some point during their treatment. Previously, the most common types of abnormality were generalised atypical spike and wave or polyspike and slow wave of varying frequency. Similar abnormalities could be present at all dosages but in

a much reduced form. It was noted that slow waves were particularly responsive to treatment. The provocative effect of eye-closure for evoking abnormalities decreased with increased dosage of sodium valproate. Withdrawal of the drug brought a speedy return to the pre-drug levels.

6.4.2. Background activity.

The spontaneous background EEG activity was taped onto a Fenlow F.M. magnetic tape recorder from the left and right occipito- central (O_1 - C_3, O_2 - C_4). derivations using a parasaggital montage (see Fig. 6. 4.). The total EEG and alpha component have been reported to appear with greater amplitude over the occipito-parietal region than the parietal-central area (Butler and Glass 1974) so that bipolar recording from the occipital to central records was intended to produce a general but well-defined estimate of the EEG signal. Also, these derivations were chosen for automatic EEG analysis due to the prominence of abnormalities within the posterior region during IPS.

One minute of EEG activity with eyes-closed was recorded prior to hyperventilation, and similarly the last minute of hyperventilation. Period analysis was later carried out on a DEC-PDP8 computer with automated punched paper-tape output. Both EEG channels were analysed for each condition in a 50 second epoch.

Period analysis measures the amount of time occupied by each wave crossing the base-line (zero-crossings). The EEG frequencies are transformed into square waves which produce signals at each instance where the original waveform crosses the base-line. The time between signals (period) is automatically enumerated giving the number of half cycles for

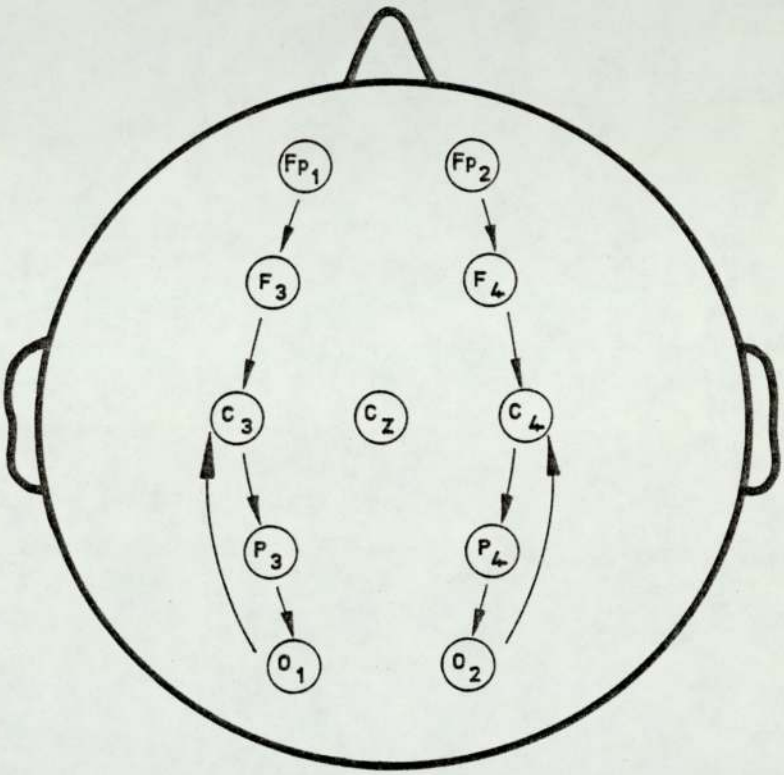


Fig. 6.4. Parasaggital Montage

each frequency. Unfortunately, period analysis does not account for amplitude. If the amplitudes of the frequency components are similar, the faster frequencies dominate the final result. Also, components superimposed on high amplitude slower frequencies do not cross the base-line and are unscored. Similarly, harmonically modulated waveforms are not differentiated. Frequencies above a certain amplitude can only be measured as 'noise' and slight drifts of DC level need to be disregarded (Harding 1968).

The punched paper tape of period analysed EEG data was fed into a DEC-PDP15 computer, where the number of half-cycles for delta (1 - 3 c.p.s.), theta (4-8 c.p.s.), alpha (9 - 13 c.p.s.) and beta (14 - 32 c.p.s.) were computated as frequency indices and listed onto a patient file.
For each patient, at pre-drug, optimum dosage and post-drug investigations, similar recordings and period analyses were made on sex and age matched control subjects obtained from schools, youth organisations and colleges in the Birmingham area. All comparisons between patients and controls were made using the results obtained over the non-dominant hemisphere. Studies have shown that the dominant hemisphere may be more affected by lateralisation effects. Clarke and Harding (1969) found that while monozygotic twins were more alike in the EEG than dizygotic twins, this factor was particularly applicable to the non-dominant hemisphere. Butler and Glass (1974) reported that the total EEG had an asymmetric distribution between homologous areas of the cerebral hemispheres and believed it to be associated with handedness. Activity was significantly smaller in the dominant hemisphere. As asymmetries in alpha rhythm were more indicative of lateral-

isation in verbal processing, these authors also suggested that the presence of a potential converser in the recording situation had the effect of maintaining a state of readiness in the verbal (dominant) hemisphere, thus creating relative suppression over this region.

Controversy exists as to whether EEG activity is normally distributed. Some authors have employed parametric statistics (Johnson and Ulett 1959; Taistra, Gerken and Doose 1976) but others observed a non-normal distribution with regard to frequency (Hawkes and Prescott 1973) and large individual differences in skewness and kurtosis of the frequency spectrum (Grosveld, DeRijke and Vissel 1976). With large samples parametric tests may be applied in accordance with the central limit theorem; the test can be applied despite a missing normal distribution if there is a sufficient number of degrees of freedom. However, in the present study only a limited number of patients was available for analysis which meant that sub-division into those with normal and abnormal EEGs invalidated the use of parametric tests, due to small samples. Comparisons within patients, and between patients and matched controls, were therefore made using the Walsh test (Siegel 1956), a non-parametric test for two related samples.

All EEG recordings were made under standardised conditions (see Section 6.3.). Although individual differences do occur in the stability of the EEG between repeat investigations, high coherence is found in the occipital area (Johnson and Ulett 1959). Functional changes in women may be dependent on the menstrual cycle in that an acceleration of alpha activity has been found during the cycle (Creutzfeldt, Arnold, Becker, Langenstein, Tirsch, Wilheim and Wuttke 1976).

However, in women taking the contraceptive pill a reduction in mean alpha frequency was evident. Overall, skewness and kurtosis were found to be stable parameters in most individuals.

6.4.2.1. Period analysis.

The spontaneous background EEG activity was analysed for 13 patients prior to sodium valproate treatment, for 14 patients at optimum dosage who had attained a significant improvement in photosensitivity, and for 11 of these patients after withdrawal of treatment. Comparisons were made with sex and aged matched control subjects at each stage of therapy.

At the last EEG before the commencement of sodium valproate, the age range of patients was from 7 years 4 months to 21 years 7 months (mean 15 years 3 months, S.D. 4 years 1 month). The mean age of paired controls was 15 years 5 months (S.D. 4 years 2 months). Three patients had abnormal resting EEGs (i.e. before hyperventilation) and in 10 patients there was no evidence of spike and wave or non-specific abnormality. No significant differences were found between the 10 patients with normal EEGs and controls, for the total EEG index (zero-crossings) or individual waveforms ($P > 0.05$). Five of these patients were receiving anticonvulsants.. When they were excluded from analysis, it was found that the alpha index was significantly greater (Walsh test, $P = 0.031$) and the delta index significantly lower (Walsh test, $P = 0.031$) in the non-medicated patients than controls. This latter result should be viewed with caution as more artefactual slow-drift potentials were probably present in the EEGs of controls receiving their first EEG investigation.

During hyperventilation, no significant differences were seen in the total EEG activity or delta, theta, alpha and beta rhythms between 5 patients with normal EEGs and paired

controls ($P > 0.05$), or between the 8 patients with an a normal overbreathing response and controls ($P > 0.05$). Similar results were obtained when 5 of these latter patients, who were receiving anticonvulsants, were excluded from analysis ($P > 0.05$).

After a period of sodium valproate treatment ranging from 2 months to 2 years 3 months (mean 11.57, S.D. 7.91 months), 6 patients were receiving 1000 mgm., 5 patients 1200 mgm., 1 patient 1400 mgm., 1 patient 1600 mgm. and 1 patient 600 mgm. daily at optimum dosage. One patient on 1200 mgm. also received a single 10 mgm. dose of imipramine. Before hyperventilation, only 1 patient showed spike and wave abnormality. Although no significant differences were found between the patients with normal resting EEGs and controls for the total amount of EEG activity, the alpha index was significantly reduced in patients (Walsh test, $P = 0.047$). No significant differences were seen for beta, delta or theta activity, although the latter rhythm was slightly increased in patients.

In the 11 patients with normal EEGs during hyperventilation, no significant effect was seen in the total EEG or for alpha, theta, and beta waveforms, although the theta and beta indices tended to be greater in the photosensitives. However, the delta index was significantly lower in patients (Walsh test, $P = 0.048$), which again may have resulted from slow wave artefact in the EEGs of control subjects. The background activity in the 3 patients with EEG abnormalities induced by hyperventilation, showed no marked differences from that of control subjects. However, delta and theta rhythms were slightly increased and alpha and beta reduced in patients. None of the 3 patients were receiving additional anticonvulsants.

Analysis of the post-drug EEG was conducted 1-7 months after withdrawal of sodium valproate (mean 3.0, S.D. 1.81 months). The ages of patients now ranged from 7 years 11 months to 22 years 10 months (mean 13 years 10 months, S.D. 3 years 8 months). The mean age of matched controls was 14 years, 4 months (S.D. 3 years 11 months). At withdrawal of sodium valproate, 3 of the 11 patients were reinstated on phenobarbitone (30 mg/day). Eight patients had a normal EEG before hyperventilation. No overall significance was observed between these patients and controls in the total EEG index. Delta, theta and alpha waveforms were also similar in both groups ($P > 0.05$). However, the photosensitive patients had a significantly greater beta index (Walsh test, $P = 0.043$). When 2 patients (with normal EEGs) receiving phenobarbitone were dropped from analysis, again the indices for total EEG, delta, theta and alpha remained non-significant, but beta activity was still significantly greater in patients than in controls. This effect could not therefore be attributed to medication.

At the post-drug investigation, hyperventilation failed to evoke abnormality in 3 patients. Although no significant differences occurred for total EEG analysis or delta, theta and alpha waveforms, the beta index was consistently increased in all 3 cases in comparison to control subjects, although no anticonvulsants were being taken. However, comparison between the 8 patients with abnormal EEGs during hyperventilation and controls produced no significant differences in the overall background EEG or for any specific waveform, even when the 3 patients receiving phenobarbitone were excluded from analysis ($P > 0.05$).

The direct effect of sodium valproate treatment was tested by intra-subject comparisons. Seven patients had undergone automatic EEG analysis at the pre-drug and optimum dosage EEG. Before hyperventilation, the EEG showed no significant differences in totalactivity or indices for delta theta, alpha and beta range ($P > 0.05$). However, delta activity was slightly increased during the pre-drug EEG, theta and beta activity at the optimum dosage investigation, and alpha activity showed negligible variation. No overall or specific significant differences were observed during hyperventilation before or after successful sodium valproate treatment ($P > 0.05$). Of the 7 patients, 5 were receiving anticonvulsants before the commencement of sodium valproate. No additional medication was taken at optimum dosage.

Comparison of the background activity between optimum dosage and the post-drug EEG was available for 6 patients. All patients were free from other anticonvulsants at both investigations. No significant alteration had occurred in the pre-hyperventilation record for overall EEG activity or specific waveforms ($P > 0.05$), although theta was still somewhat increased at optimum dosage and beta activity was greater at the post-drug EEG. No significant differences were found between the background EEGs during hyperventilation ($P > 0.05$).

In conclusion, patients prior to sodium valproate therapy who were not receiving other medication were found to have significantly more alpha activity in their resting (i.e. pre-hyperventilation) records than normally seen in non-photosensitive controls ($P = 0.031$). However, individual differences in the amount of EEG activity between repeat EEGs were found by Johnson and Ulett (1959), using parametric t tests,

to be due to a significantly reduced response at the first recording. As mentioned previously, control subjects only received a single EEG investigation and alpha activity occurs with greatest intensity over the posterior EEG derivations (Butler and Glass 1974). However, this does not explain why at optimum dosage of sodium valproate, patients' resting EEGs now contained significantly less alpha activity than control subjects ($P = 0.047$). Within patient comparisons showed that, in fact, neither the total EEG index nor any specific waveform had been significantly changed by sodium valproate treatment, although theta activity had slightly increased. At times, control subjects were found to have significantly greater amounts of slow wave activity in their background EEGs but this was probably due to slow-drift artefacts through head movements.

Hyperventilation produced no significant difference in the EEG between patients and controls, which neither varied significantly from pre-drug or post-drug observations. Changes associated with hyperventilation are complex, and generally an increase in the amplitude of the dominant activity occurs which is usually followed by a gradual increase in the slower frequencies (Corbin et al. 1955). Although the final minute of hyperventilation was analysed, period analysis does not incorporate amplitude changes. Also, in the photosensitive patients the EEG abnormalities only occupied a small percentage of the sampled EEG. The frequency of spike abnormality also tends to lie in the range of faster frequencies insensitive to automatic analysis (Corbin et al. 1955).

After withdrawal of sodium valproate, the background EEG of patients both before and during hyperventilation contained

significantly more beta activity than seen in control subjects, which was not attributable to barbiturate medication. However, although this effect was also evident from within patient comparison between the optimum dosage and post-drug EEG, it was non-significant. The amplitude of the cortical EEG obviously influences EEG amplitude recorded at the scalp by surface electrodes. However, more important is the cortical area involved and the degree of synchrony in electrical activity over this area (Cooper, Winter, Crow and Walter 1965). Small time differences, therefore, between the occurrence of similar waves in adjacent cortical regions will effectively reduce the amplitude of the scalp EEG. Also, a given time difference in wave occurrence will have a much greater cancelling effect on higher frequency activity than on slower rhythms. These authors propose that this explains why most of the frontal beta activity detected by intracranial electrodes is generally not clearly seen on the scalp. If after sodium valproate withdrawal synchrony of cranial beta activity was increased over the frontal and central areas, this would register in the posterior derivations (O1 - C3 and O2 - C4) due to minimal low voltage fast activity (LVFA) at the occiput.

In patients who retained abnormal EEGs, before or during hyperventilation, no significant differences were found at any stage of sodium valproate treatment for changes in total activity or specific waveforms of the background EEG.

In general, therefore, period analysis showed no conclusive differences between photosensitive patients and their normal peers as regards spontaneous background activity of the EEG; neither did automatic computation illustrate a significant effect of sodium valproate treatment in the photo-

sensitive EEG, which is in agreement with the Fau and Garrel (1968) and De Biolley and Sorel (1969b) reports of non-photic epilepsies. However, unlike barbiturate medication, sodium valproate did not produce LVFA in the EEG which supports the findings of Miribel and Marinier (1968). In fact, there was an indication of increased theta activity in the normal resting record during treatment and an increase in LVFA as a result of sodium valproate withdrawal.

6.5. Sex Differences.

Prior to sodium valproate therapy, 19 females and 17 males had some degree of abnormality in their basic EEG. There were no overall significant differences between the two sexes as regards basic record normalisation or the rate of normalisation in those patients attaining a significant improvement in photosensitivity, (Fisher-Yates Contingency tests, $P > 0.05$ respectively).

Female patients were classified according to the phase of their menstrual cycle (when known) at the last pre-drug investigation and at optimum dosage. Due to the low numbers in each group, two major divisions - i.e. Low Oestrogen (pre-menstrual and menstrual phases, together with the seven 'no menarche' patients) and High Oestrogen (i.e. preovulatory, ovulatory and luteal phases) were compared using Fisher-Yates contingency tests. Neither before treatment or at optimum dosage of sodium valproate were there any significant differences between the two menstrual phase groups as regards the incidence of normal or abnormal basic EEGs ($P > 0.05$ respectively). These tests were repeated for Low Progesterone (menstrual, preovulatory, ovulatory and premenstrual phases, together with the 'no menarche' patients) and High Progesterone (luteal phase). Again, the results were non-significant (Fisher-Yates Contingency tests, $P > 0.05$).

In conclusion, sodium valproate has no differential effects on the basic EEGs of males and females, neither is there any indication that the drug's effectiveness is influenced by sex hormones.

6.6. Clinical Differences.

Of the 50 patients studied, 48 were classifiable into standard clinical groups. One female patient, aged 7 years 4 months before treatment, was the sister of one of the photosensitive epileptic patients, and had no history of fits but was being treated prophylactically for photosensitivity during IPS. She also had an abnormal EEG. Another photosensitive patient had a clinical history of syncope but with no direct evidence of precipitation by flickering light. Her basic EEG prior to commencement of sodium valproate was normal.

A clinical history of fits precipitated by flicker (Group I) had occurred in 22 patients. Photosensitive fits and spontaneous epileptic attacks (Group II) were reported by 16 patients and spontaneous fits only, without any implication of flicker stimulation (Group III), previously occurred in 10 patients. Before sodium valproate treatment, the frequency of spike and/or spike and wave abnormalities was significantly greater than the incidence of normal EEGs in Group II (χ^2 = 3.27 df1, P = 0.05) and Group III (χ^2 = 2.78 df1, P = 0.05). However, no significant difference occurred within Group I patients (χ^2 = 0.88 df1, P > 0.05).

At optimum dosage, the number of normal basic EEGs now became significantly greater than abnormal EEGs in both Group I (χ^2 = 5 df1, P = 0.025) and Group II (χ^2 = 4 df1, P = 0.025). No significant difference was seen within Group III (χ^2 = 0.11 df1, P > 0.05). However, as the incidence of spontaneous abnormality had previously been high for Group III patients, it was evident that in all groups movement had occurred towards the normalisation of basic EEG activity.

Seizure Type	No. in Sample	Percentage
Tonic - Clonic	43	86 °/o
Absences	10	20 °/o
Myoclonic Jerks	7	14 °/o
Eyelid Myoclonia	6	12 °/o
Psychomotor	5	10 °/o
Myoclonic Akinetic	3	6 °/o
Mixed Seizures	18	36 °/o
Syncope	2	4 °/o
No Fits	1	2 °/o
Compulsive T.V. viewing	10	20 °/o

Table 6.3. Distribution of Clinical Seizures

At the pre-drug investigation, 34 of the 36 patients with some form of EEG aberration were clinically classifiable. No significant difference occurred between purely photosensitive epileptics (Group I) and those with spontaneous fits, with or without additional attacks induced by flickering light (Groups II and III), as regards the overall frequency of basic EEG normalisation throughout the duration of treatment; neither was there a significant difference between these two divisions for the rate of normalisation in relation to the attainment of a significant improvement in photosensitivity. (Fisher-Yates Contingency tests, $P > 0.05$ respectively).

Table 6.3. shows the distribution of seizures amongst the 50 photosensitive patients. Overall 31 patients had a clinical history of purely generalised seizures, 3 had minor seizures and 11 patients suffered generalised convulsions together with focal and/or minor seizures. Prior to treatment with sodium valproate 20 generalised epileptics, 3 minor epileptics and 11 patients with mixed seizures had either spike, spike and wave or non-specific EEG abnormalities. During treatment, the frequency of EEG normalisation was 65%, 67% and 64% respectively. It was evident that no significant differences existed between the various seizure-type groupings in the normalisation of the spontaneous EEG (Fisher-Yates Contingency test $P > 0.05$).

6.7. The Visual Evoked Potential.

Controversy has existed as to the nature of the visual evoked potential (VEP) in photosensitive epilepsy. The major problems producing variable results appear to be the use of too few subjects and differences in recording techniques. Early literature found that the photosensitive VEP was similar to that seen in other epilepsies (Černáček and Cigánek 1962), and that it was abnormal and of high amplitude (Lücking et al. 1970; Crighel et al. 1974) even when patients' EEGs were normal, (Bablouzian et al. 1969). However, others noted that the presence of seizure activity altered VEP morphology (Gastaut and Régis 1964; Rodin et al. 1966), and Chatrian et al. (1970b) found essentially normal responses in two pattern-sensitive epileptics during the absence of spike and wave discharge. Although authors believe the photosensitive VEP to be essentially similar in morphology to that of normal subjects (Hishikawa et al. 1967), disagreement exists as to the latency and amplitude changes of particular components (Gastaut and Régis 1964; Hishikawa et al. 1967; Bablouzian et al. 1969).

A characteristic feature of a proportion of photo-sensitive patients is the presence of occipital spikes. Conjecture arose as to the relationship of this abnormality to standard VEP components. Hishikawa et al. (1967) believed that the occipital spike represented an enhancement of early negative components. However, Panayiotopoulos et al. (1970; 1972) found that the latency for the negative polarity of the occipital spike remained consistent around 94-118 msec., even at flash rates where the inter-stimulus interval was shorter than latency. Although they failed to agree with Hishikawa

and his colleagues, their indication that the occipital spike might be related to the triphasic Vab component reported by Gastaut and Régis (1964) was later supported by Dimitrakoudi et al. (1973). The use of a high intensity light and fine grid pattern produced an increased incidence of occipital spikes which appeared to develop from the descending arm of the major inhibitory component (P2) with increase in flash rate. Occipital spikes were therefore believed to result from a failure of normal inhibitory mechanisms (Jeavons and Harding 1975), (see Section 2.6.2.).

6.7.1. Recording technique.

Visual evoked potentials were recorded on 25 photosensitive patients attending the Neuropsychology Unit. EEG recording was made on an S.L.E. 12-channel machine using scalp silver-silver chloride electrodes placed according to the 10/20 system (see Fig. 6.4.). The overall time constant of the system was 0.3 sec., gain 100 uv/cm. and paper speed of 30 cm/sec. High frequency filters were rarely used as the subject was always encouraged to relax.

Two channels were selected for analysis. Bipolar recording was made from either the right or left occipito-central derivations ($O_2 - C_4$ or $O_1 - C_3$) from a parasaggital montage, depending on which was the non-dominant hemisphere (see Section 6.8.). Buchsbaum and Fedio (1969) found that averaged VEPs reflected lateralised cerebral activity with regard to verbal and non-verbal functions. Designs appeared to be mediated by the non-dominant hemisphere and words by the dominant hemisphere. However, better VEP replication for both types of stimulus were seen within the non- dominant hemisphere, indicating less differentiation and greater

uniformity of response. Previous work by the present author showed that occipital spikes, although evident over both cerebral hemispheres, at times tended to be of greater amplitude over the non-dominant hemisphere (Herrick 1973).

Evoked potentials were summated using a Computer of Average Transients (CAT.400C). As prolonged IPS, particularly at increased flash rates, is potentially hazardous to photosensitive patients, summation was taken over 25 sweeps each sampling 500 msec. of EEG activity after the onset of each flash. The CAT was externally triggered by the output of the Grass PS22 stroboscope, after the presentation of a few flashes to the subject in order to avoid summation of the initial on-response. One channel of the CAT displayed the summated VEP and a second channel monitored the flash rate. A permanent record was obtained on a Hewlett-Packard X-Y plotter.

During photic stimulation the patient lay in a supine position in a sound damped, dimly lit room of 4.6 nits background illumination. In order to provide maximal stimulation of the visual pathway, the patient was instructed to view the centre of the stimulus, on which lay a small open-ring fixation point, placed at 31 cms. from the patient's eyes. At this distance the stimulus subtended a 24° visual angle. Drasdo (1977) developed a formula for determining the neural representation Q of a circular stimulus at θ° subtense,

$$Q = 100 \left[1 - \exp(-0.0574\theta) \right]$$

Therefore at a 24° visual angle the concentric lamp stimulated exactly 75% of the visual information channel capacity. To encourage occipital spikes, a fine black-lined grid pattern (Normatone HN 560) of 26' square subtense was superimposed on the high intensity diffused blue-white flash of 10 µsec. duration at 1,363 nits (Grass intensity 2). The grid pattern allowed

40% transmission of the plain diffused flash. VEPs were also recorded using only the diffused light stimulus at each flash frequency as an aid in clarifying standard components and the presence or absence of occipital spikes with the grid patterned flash.

At each investigation, the VEP was recorded at 1, 3 and 5 f.p.s. Evoked driving potentials and occipital spikes were optimally recorded at 7 and 9 f.p.s., Odd numbered frequencies were used to minimise the generation of harmonic responses. In some patients, where PCRs occurred at 9 f.p.s. and at lower rates, recording was made using short and intermittent trains of flashes in an attempt to avoid spike and wave contamination of the averaged evoked potential. Before each investigation, the X-Y plotter was calibrated for latency measurements, and afterwards 5μv, calibration signals were recorded for amplitude measurements.

Age and sex matched controls were investigated for each patient before, during and after withdrawal of sodium valproate. All controls underwent the same recording procedure. However, whereas patients were used to the laboratory setting, the majority of control children could only undergo a single recording. Before agreeing to take part in the study, control subjects were well informed of the experimental procedures, and the actual recording session was made as interesting as possible for the children, to reduce any tension and maintain their co-operation.

The general morphology and nomenclature of VEP components (after Harding 1974) is shown in Fig. 2.1.. N refers to a negative going wave and P to a positive polarity. Amplitudes are described as peak - trough or trough - peak measurements. The a priori selected level of significance

(α) for latency (msec.) was α = 0.05 and for amplitude (μv.), α = 0.01. The higher probability level for amplitude was chosen due to the multitude of variables, e.g. fatigue, direction of gaze, habituation, which could affect the size of the VEP. The following analysis is based on the VEPs recorded at 1, 7 and 9 f.p.s..

6.7.2. Effect of sodium valproate.

Visual evoked potentials were recorded in 25 photosensitive patients, mean age 14 years 1 month (S.D. 4 years 3 months) before commencing sodium valproate treatment. Similar recordings were made in 21 of these patients after reaching a significant improvementin photosensitivity at optimum dosage of sodium valproate. The mean duration of treatment at this stage was 9.52 months(S.D. 6.38 months). Results were also obtained for 9 patients after a mean withdrawal period of 1.78 months (S.D.1.23 months). Before and after treatment with sodium valproate, photic stimulation at the faster recording frequencies evoked a great deal of spike and wave contamination of the VEP in some patients, causing a reduction in the number of observations both at 7 f.p.s. and, in particular, 9 f.p.s.. There were no significant differences between the ages of photosensitive patients and matched controls at any stage of treatment (Correlated t tests, $P > 0.05$).

From the 25 patients, 9 cases underwent all levels of the investigation, i.e. pre-drug, optimum dosage and withdrawal of sodium valproate. In these patients no significant differences were found in overall latencies or amplitudes of VEP components throughout the entire study (Two-way analyses of variance, $P > 0.05$ latency, $P > 0.01$ amplitude). However, when the latencies and amplitudes of each component were compared at all three stages of treatment, the N2-P2

amplitude was found to be greater at the pre-drug EEG (mean 23.04 µv.) than at optimum dosage (mean 12.21 µv.) or after withdrawal of sodium valproate (mean 15.44 µv.) but only at the 5% level of significance ($P = 0.05$). No significant difference occurred between optimum dosage and the post-drug EEG ($P > 0.05$). Also, the P2-N3 amplitude was larger (5% level) before commencement of therapy (mean 43.78 µv.). than at optimum dosage (mean 28.41 µv.) but not significantly different from the post-drug level (mean 33.25 µv.). No significant difference was seen between this amplitude at optimum dosage and the post-drug EEG ($P > 0.05$). (Randomised block designs and Tukey's multiple comparison of means). Similar tests at 7 f.p.s. for 5 patients showed no significant differences for the latencies of N2 and P2 or amplitudes of N2 - P2 and P2 - N2. Cross comparisons at 9 f.p.s. were not possible due to insufficient observations uncontaminated by PCRs in the untreated conditions.

Although some degree of significance had been found at the 5% level, absolute rejection of the null hypothesis had previously been set at $\alpha = 0.01$. Further tests were therefore conducted using larger samples, for comparisons between patients and controls, and two-way comparisons within the patient drug-regime, e.g. pre-drug to optimum dosage.

6.7.2.1. Pre-drug VEP.

Before the commencement of sodium valproate treatment, 12 patients were taking other drugs and the remainder received no medication. Two patients were taking two anticonvulsants and the other 10 patients one drug. Six patients received phenobarbitone, 5 patients phenytoin, and ethosuximide, imipramine, and sodium amytal each by 1 patient

respectively. There was no significant difference between the ages of the medicated and non-medicated patients (Independent t test, $t = 1.69$ df 23, $P > 0.05$). Two-way analyses of variance showed no significant differences between the two groups as regards latency and amplitude of all VEP components.

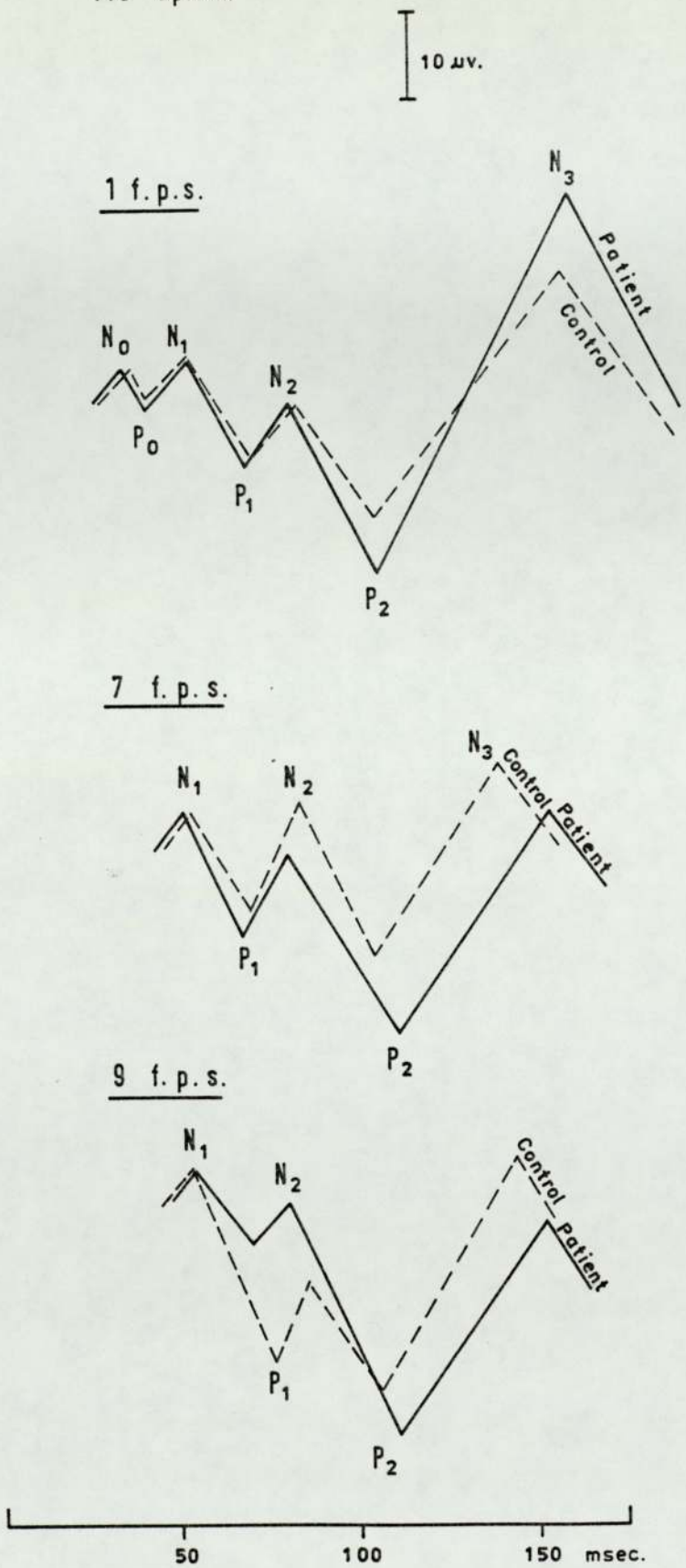
Comparison was made between the 25 photosensitive patients at the pre-drug EEG and their matched normal contacts (see Fig. 6.5.). No significant differences were seen in VEP component latencies at 1 f.p.s. (Two-way analysis of variance $P > 0.05$). However, a significant increase of the overall VEP amplitude was evident in the photosensitive patients ($P = 0.01$). A priori correlated t tests had shown that this was attributable to the significantly greater amplitudes of N2 - P2 (19.47 μv.) and P2 - N3 (42.38 μv.).

Evoked potentials were obtained for 14 patients at 7 f.p.s. and for 6 patients at 9 f.p.s. Neither component latencies nor amplitudes differed significantly from those of control subjects (Two-way analyses of variance, $P > 0.05$ respectively). Fig. 6.5. shows the mean latencies and amplitudes at 7 f.p.s. for patients and controls.

6.7.2.2. Optimum dosage VEP.

At optimum dosage one patient received 600 mgm., 2 patients 800 mgm., 9 patients 1000 mgm., 7 patients 1200 mgm., 1 patient 1400 mgm. and 1 patient 1600 mgm. daily of sodium valproate. Two patients also received reduced dosages of other drugs. A single nightly dose (10 mgm.) of imipramine was taken by one patient with enuresis. Another patient continued with a nightly dose of tryptosal.

Pre Epilim



		Patients		Control	
		$\bar{X}$	S.D	$\bar{X}$	S.D.
N_0 *	Lat.	33·4	5·7	36·1	6·6
	Ampl.	4·4	2·2	3·4	4·5
P_0	Lat.	40·4	9·2	39·3	7·8
	Ampl	5·4	3·9	3·4	1·6
N_1	Lat.	51·7	7·6	50·5	5·4
	Ampl.	12·1	7·6	11·0	8·5
P_1	Lat.	69·1	10·1	69·7	8·6
	Ampl.	7·6	6·8	5·7	6·5
N_2	Lat.	81·7	6·8	82·5	8·6
	Ampl.	19·5	13·2	13·3	8·7
P_2	Lat.	105·8	11·5	105·1	9·0
	Ampl.	42·4	27·1	27·4	15·2
N_3	Lat.	157·9	16·9	156·8	18·5
	Ampl.	24·2	29·0	21·5	21·5

N_1	Lat.	51·0	9·0	53·0	4·7
	Ampl.	14·3	12·1	11·7	6·6
P_1	Lat.	67·1	10·1	70·1	8·7
	Ampl.	9·5	9·0	12·4	8·9
N_2	Lat.	79·9	9·2	82·7	6·8
	Ampl.	21·0	14·0	17·3	10·9
P_2	Lat.	111·2	7·9	104·1	9·2
	Ampl.	25·9	15·3	22·3	16·4
N_3	Lat.	152·6	17·4	139·7	17·4
	Ampl.	-	-	-	-

N_1	Lat.	52·7	8·6	52·5	5·4
	Ampl.	8·4	6·1	22·0	16·5
P_1	Lat.	69·6	7·9	75·3	1·9
	Ampl.	5·2	3·7	8·8	8·6
N_2	Lat.	80·5	8·1	85·0	3·7
	Ampl.	25·8	8·3	12·7	12·2
P_2	Lat.	110·1	10·3	106·5	5·3
	Ampl.	24·9	5·4	26·5	14·6

* eg. No Ampl. = No – Po Amplitude

Fig. 6.5. Visual Evoked Potentials at 1, 7 and 9 f.p.s. for Photosensitive patients, before Sodium Valproate treatment and Normal controls.

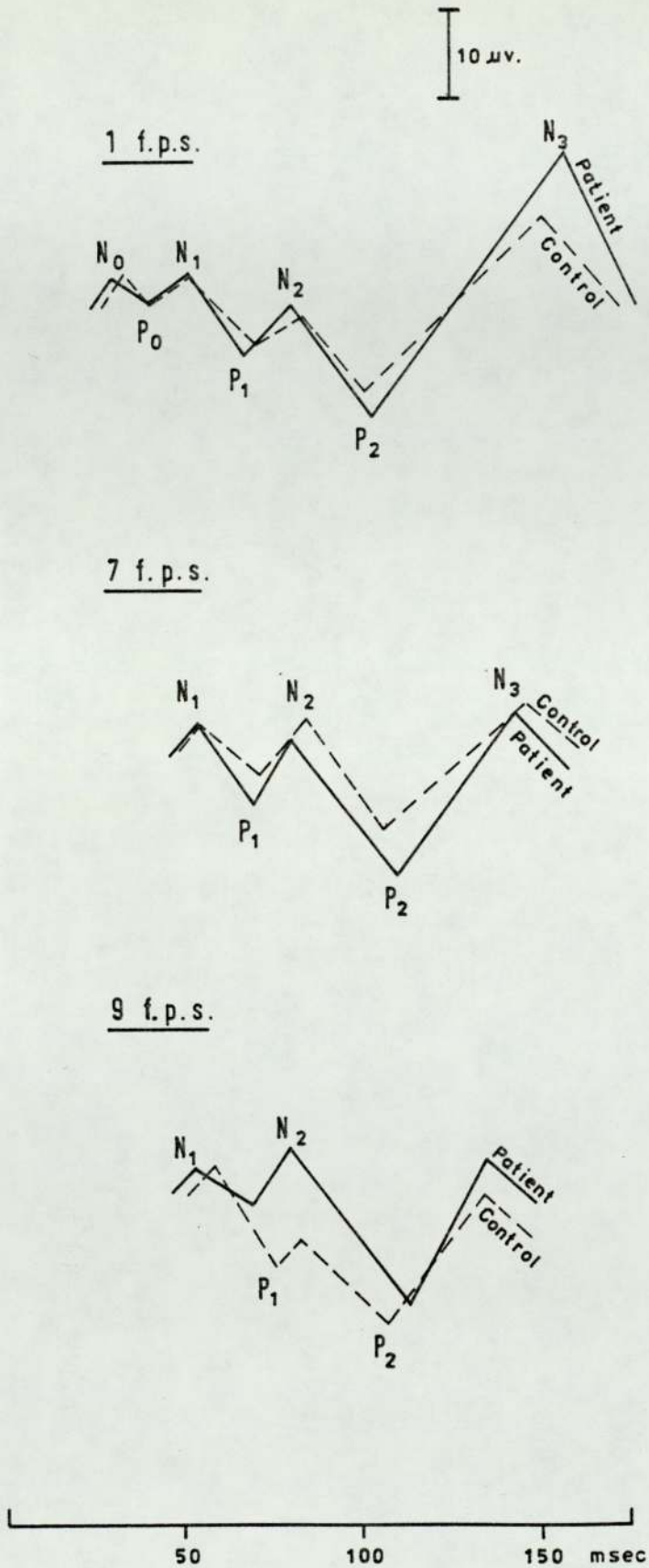
A two-way analysis of variance for VEP component latencies showed no significance between patients and controls. However, the overall amplitude of the VEP, in particular N2-P2 and P2 - N3, remained significantly greater in photosensitivies (1% level) (see Fig. 6.6.) although, when pre-drug and optimum dosage VEPs were compared within patients, a significant reduction was seen in the N2 - P2 ($t = 2.79$ df 18, $P = 0.01$) and P2 - N3 ($t = 2.58$ df19, $P = 0.01$) amplitudes during sodium valproate treatment (see Fig. 6.7.). No significant change had occurred in the latencies of VEP components.

VEPs were obtained in 20 patients at 7 f.p.s., as the presence of PCRs in 1 patient only allowed recording up to 5 f.p.s., and 18 patients were tested at 9 f.p.s.. Although the N2-P2 and P2-N3 amplitudes were somewhat increased in patients when compared to control subjects, no significant differences were found in latency or amplitude of the VEP, (see Fig. 6.6.); neither had any component in the photosensitive VEP altered significantly in latency or amplitude when compared to pre-drug measurements (Two-way analyses of variance, $P > 0.05$), (see Fig. 6.7.).

6.7.2.3. Post-drug VEP.

After withdrawal of sodium valproate, no significant differences were found between patients and controls at 1 f.p.s., 7 f.p.s. and 9 f.p.s. for latency or amplitude of all VEP components, (Two-way analyses of variance, $P > 0.05$). However, at 7 and 9 f.p.s. the N2-P2 amplitude tended to be of greater amplitude in the photosensitives (see Fig. 6.9.). It was also found that no VEP component, measured at these flash frequencies, had altered significantly in latency or amplitude between the optimum dosage and post-drug or pre-drug and post-drug investigations ($P > 0.05$).

Optimum Dosage



		Patient		Control	
		$\bar{X}$	S.D.	$\bar{X}$	S.D.
N_0 *	Lat.	34·1	5·5	30·9	6·7
	Ampl.	2·3	2·2	2·6	1·2
P_0	Lat.	41·6	7·0	40·5	6·6
	Ampl.	3·6	2·5	3·1	2·7
N_1	Lat	52·6	6·6	52·7	5·0
	Ampl.	8·8	4·2	7·9	5·1
P_1	Lat	67·5	9·9	71·1	5·6
	Ampl.	5·8	3·5	3·6	2·4
N_2	Lat.	79·6	9·5	83·1	8·2
	Ampl.	12·3	5·3	8·6	4·9
P_2	Lat.	102·4	8·1	101·4	6·4
	Ampl.	29·8	13·9	19·5	10·4
N_3	Lat.	155·2	19·4	149·3	11·7
	Ampl.	19·1	14·9	12·8	9·9

N_1	Lat.	53·7	8·2	54·6	4·6
	Ampl.	8·9	6·0	6·4	3·9
P_1	Lat.	69·5	9·5	72·5	4·8
	Ampl.	7·9	4·7	6·6	3·6
N_2	Lat.	79·8	8·9	84·6	3·5
	Ampl.	16·2	6·2	12·4	5·7
P_2	Lat.	109·8	9·9	106·9	8·6
	Ampl.	18·7	11·3	14·1	8·9
N_3	Lat.	142·7	18·6	145·9	21·0
	Ampl.	6·8	3·9	9·6	7·0

N_1	Lat.	56·1	8·5	58·2	5·3
	Ampl.	4·8	3·5	10·9	8·3
P_1	Lat.	68·1	9·9	75·9	3·6
	Ampl.	6·3	3·6	3·11	2·06
N_2	Lat.	79·0	8·9	83·6	6·6
	Ampl.	17·4	12·03	9·7	5·23
P_2	Lat.	113·7	10·6	107·7	6·4
	Ampl.	16·7	12·6	14·8	7·7

* eg. No Ampl. = No – Po Amplitude

Fig. 6.6. The effect of Sodium Valproate on the Visual Evoked Potential at 1, 7 and 9 f.p.s.

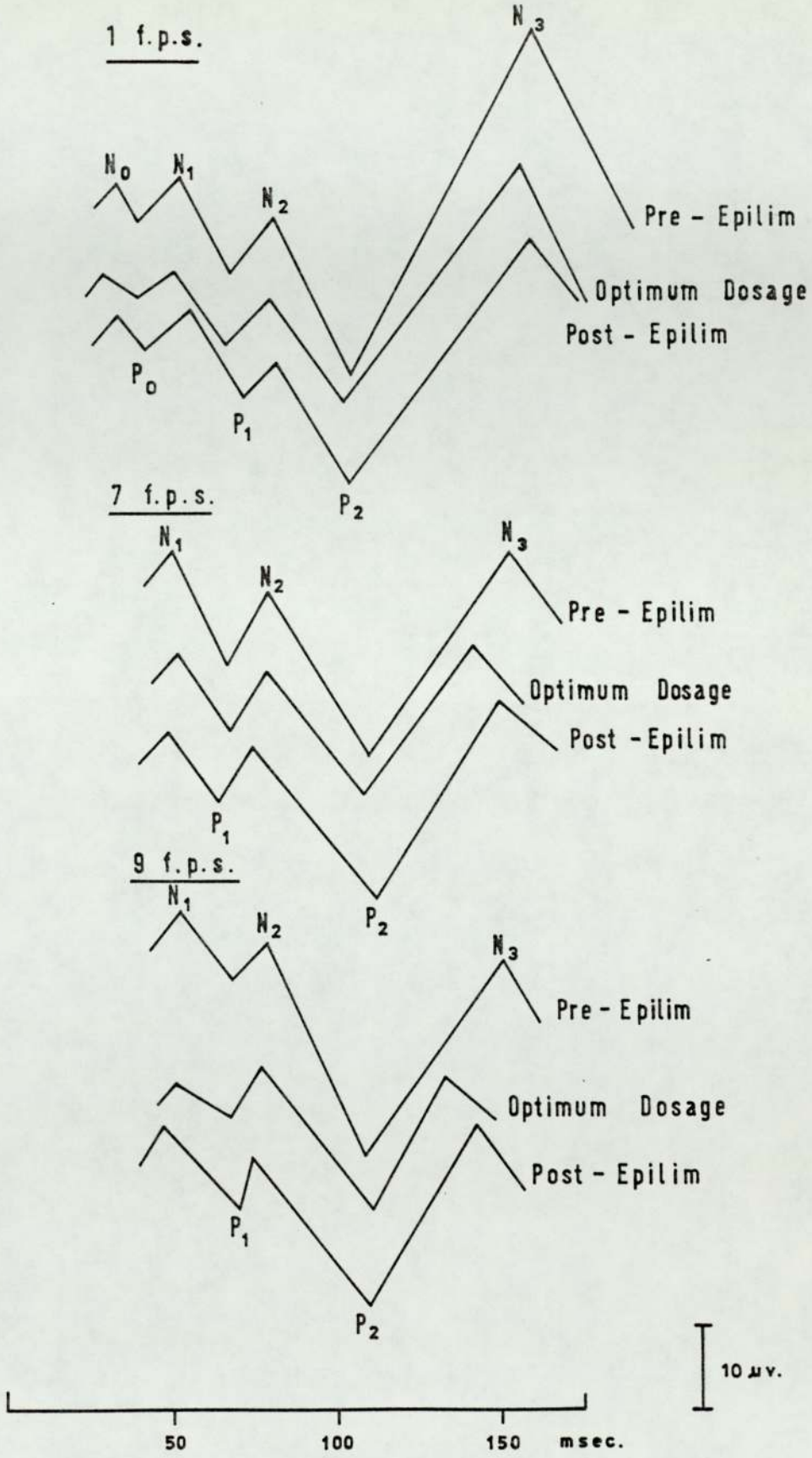


Fig. 6.7. The Photosensitive VEP at all stages of Sodium Valproate

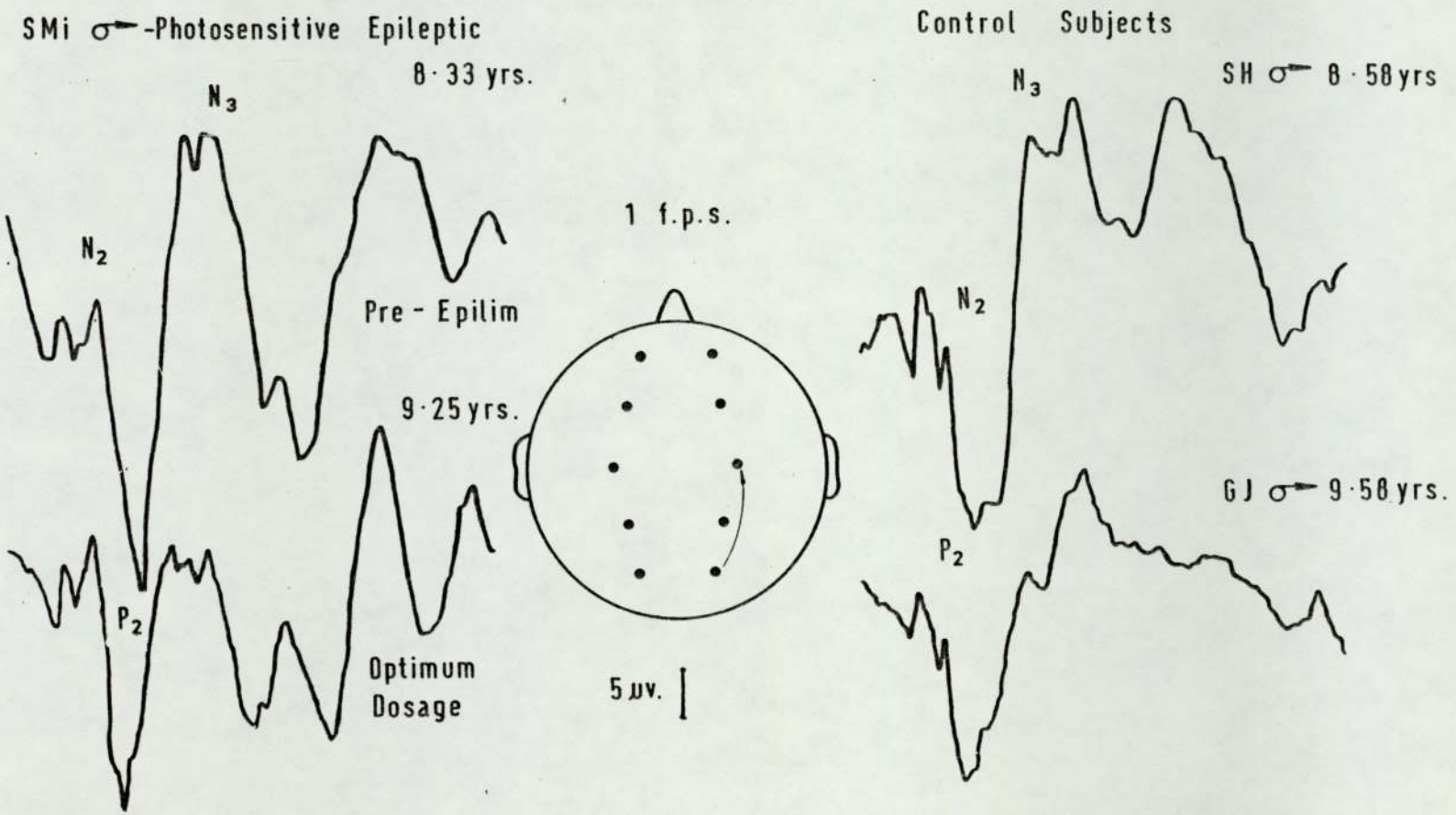
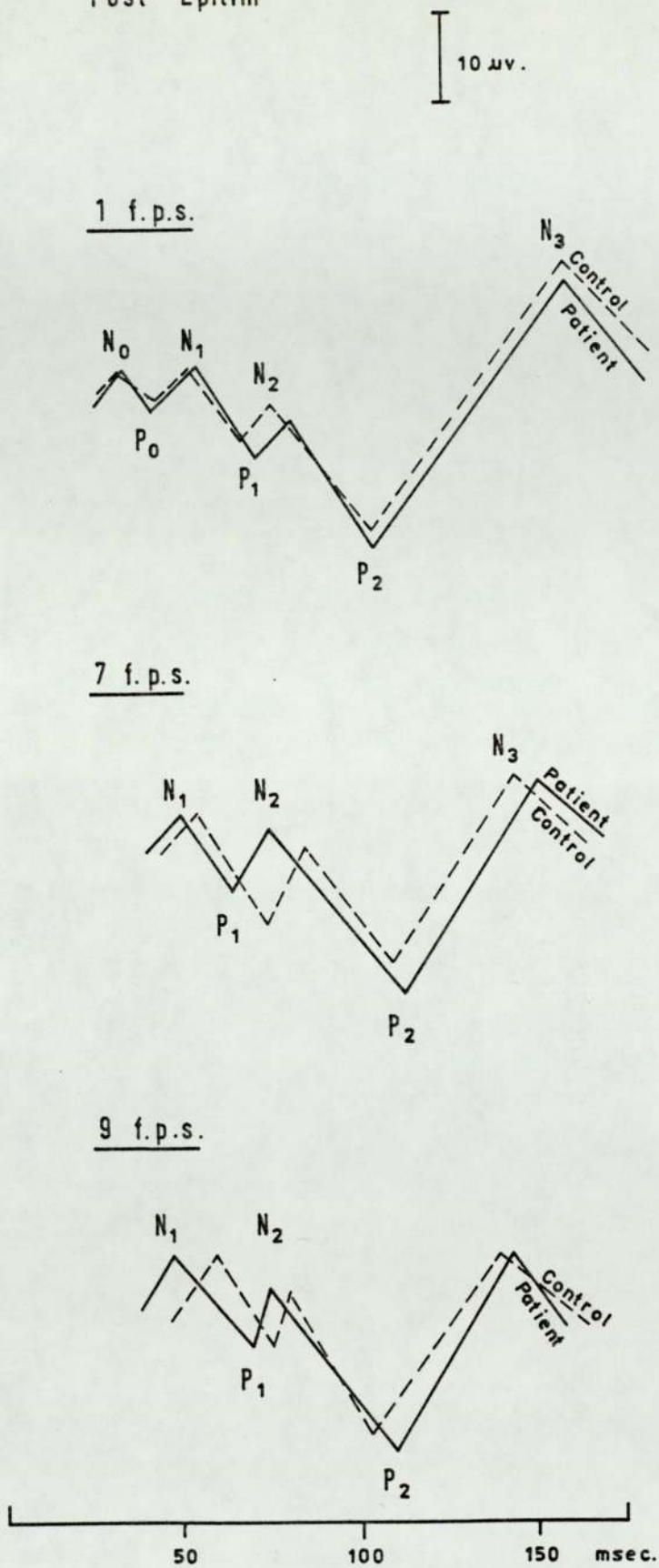


Fig. 6.8. The effect of Sodium Valproate on the Photosensitive VEP $N_2 - P_2 - N_3$ amplitude is reduced at 1000 mg/day (Optimum Dosage) but still remains greater than that of controls.

Post Epilim



		Patient		Control	
		$\bar{X}$	S.D.	$\bar{X}$	S.D.
N_0 *	Lat.	33·9	5·0	34·0	5·6
	Ampl.	3·3	1·6	4·3	2·8
P_0	Lat.	44·4	10·8	43·3	9·2
	Ampl.	3·9	1·9	4·8	2·5
N_1	Lat.	53·1	11·5	54·3	6·9
	Ampl.	8·2	4·9	10·2	4·8
P_1	Lat.	67·8	10·5	72·3	6·7
	Ampl.	4·2	4·2	4·0	2·3
N_2	Lat.	76·6	11·5	80·9	7·5
	Ampl.	14·5	7·6	14·1	6·4
P_2	Lat.	104·8	9·2	105·4	7·3
	Ampl.	31·8	10·2	31·1	12·7
N_3	Lat.	156·6	14·5	158·0	11·5
	Ampl.	22·3	8·1	14·2	6·0

N_1	Lat.	50·5	11·1	55·4	5·1
	Ampl.	9·1	4·5	13·2	12·3
P_1	Lat.	66·1	13·0	75·3	3·4
	Ampl.	7·3	4·9	8·6	5·2
N_2	Lat.	75·9	11·8	85·6	4·1
	Ampl.	19·3	7·7	13·7	4·5
P_2	Lat.	113·1	7·6	110·1	8·7
	Ampl.	24·4	10·0	21·4	11·8
N_3	Lat.	105·6	16·0	145·3	10·0
	Ampl.	-	-	-	-

N_1	Lat.	47·7	3·3	61·3	2·9
	Ampl.	10·8	3·0	9·9	5·1
P_1	Lat.	70·3	11·6	76·3	0·9
	Ampl.	6·5	6·1	5·5	0·4
N_2	Lat.	74·3	11·8	81·8	9·4
	Ampl.	18·6	10·9	16·6	15·0
P_2	Lat.	111·8	8·1	103·0	4·9
	Ampl.	22·5	5·8	20·8	10·5

* eg. No Ampl. = No-Po Amplitude

Fig. 6.9. Visual Evoked Potentials at 1, 7 and 9 f.p.s. after withdrawal of Sodium Valproate.

Of the 9 patients recorded after sodium valproate withdrawal, VEPs were obtainable for 7 patients at 7 f.p.s. and only 4 patients at 9 f.p.s.. One patient still received her single dose of tryptosal; the other 8 patients received no medication.

6.7.2.4. Conclusions.

It should be mentioned that during every statistical two-way analysis of variance, even when no significant effect was seen between the groups under study, a high level of significance occurred between the latencies of each VEP component (1% level). Despite the normal latency variations, this shows that the VEPs, as recorded under the above procedure, were comprised of components of independent polarity.

No significant differences were found between the patients taking anticonvulsants before sodium valproate therapy and those without medication for latency and amplitude of all VEP components.

Prior to commencing sodium valproate treatment, the photosensitive VEP, at 1 f.p.s. in 25 patients, was significantly larger than that of sex and age matched controls (1% level) and this was mainly due to the increased amplitude of the major positive wave P2 (N2 - P2, P2 - N3). Although sodium valproate decreased the overall P2 amplitude significantly (1% level), the photosensitive patients still showed a greater response than control subjects. The effect of sodium valproate on P2 was still evident to some extent after withdrawal of the drug (5% level).

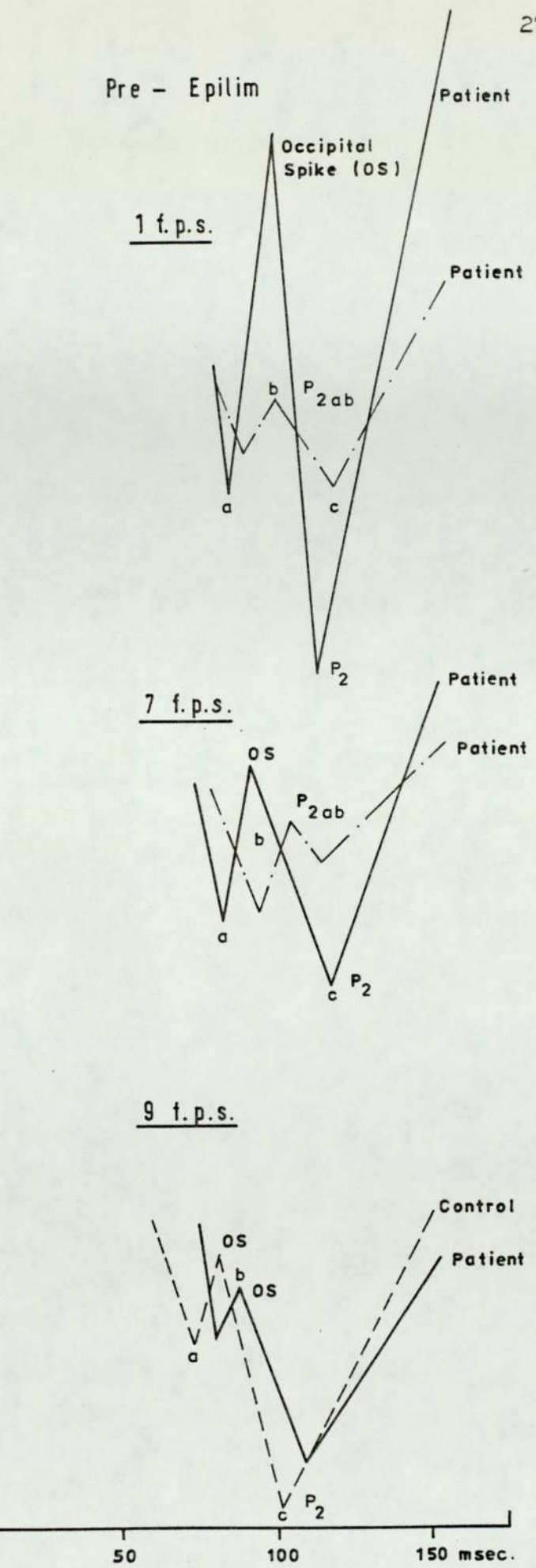
The VEP recorded at 7 and 9 f.p.s. showed no significant differences within patients before, during or after sodium valproate therapy and neither were there any differences between

patients and controls at these frequencies for latency (5% level) or amplitude (1%) at any stage of treatment. However, it was noted that the N2 - P2 and P2 - N3 amplitude at optimum dosage, and the N2 - P2 amplitude after withdrawal of sodium valproate, both at 7 and 9 f.p.s., tended to be of greater amplitude in the photosensitive VEP .

The overall lack of significance at these faster frequencies may have been influenced by the recording technique. Before and after treatment the incidence of spike and wave at 7 and 9 f.p.s. was much higher than at optimum dosage reducing the number of valid observations. However, more important, as previously mentioned, at the predrug and post-drug EEG, the short intermittent trains of flashes at 7 and 9 f.p.s. did not allow an amplitude build-up of evoked potentials often noted in the EEG of photosensitive patients. At optimum dosage it was usually possible to record the VEP at the faster frequencies in a single stimulus run due to the significant improvement that sodium valproate had exerted on the photoconvulsive response. It might have been that if this procedure had been possible in the absence of sodium valproate treatment, the increased amplitude of P2 indicated at optimum dosage could have reached a significant level within the pre-drug and post-drug VEPs.

6.7.2.5. Occipital spikes and the P2ab component.

Before sodium valproate treatment, 2 of the 25 patients showed occipital spikes in their EEG and VEP at 1 f.p.s.. Four other patients had a triphasic P2 component shown as a small positive-negative-positive wave (P2abc) occurring on the descending arm of P2 in 3 patients and on the ascending arm in 1 patient.



			Patient		Control	
			$\bar{X}$	S.D.	$\bar{X}$	S.D.
P_2	a	Lat.	90·8	8·8	–	–
	*	Ampl.	6·9	6·4	–	–
	b	Lat.	101·4	10·7	–	–
		Ampl.	11·5	9·2	–	–
	c	Lat.	118·2	11·7	–	–
		Ampl	27·7	28·7	–	–
OS	a	Lat.	86·5	5·5	–	–
		Ampl.	47·0	26·0	–	–
	b	Lat.	99·5	9·5	–	–
		Ampl.	70·3	49·7	–	–
	c	Lat.	114·5	8·5	–	–
		Ampl.	85·8	33·2	–	–
P_2	a	Lat.	94·7	9·2	–	–
		Ampl.	12·3	14·0	–	–
	b	Lat.	104·0	9·4	–	–
		Ampl.	5·2	2·7	–	–
	c	Lat.	114·3	9·7	–	–
		Ampl.	15·2	5·0	–	–
OS	a	Lat.	82·0	8·3	74·0	–
		Ampl.	20·6	12·9	24·0	–
	b	Lat.	92·8	7·4	84·0	–
		Ampl.	28·9	13·4	48·0	–
	c	Lat.	117·0	8·2	101·0	–
		Ampl.	39·8	10·1	59·5	–
P_2	a	Lat.	–	–	–	–
		Ampl.	–	–	–	–
	b	Lat.	–	–	–	–
		Ampl.	–	–	–	–
	c	Lat.	–	–	–	–
		Ampl.	–	–	–	–
OS	a	Lat.	80·0	14·0	73·0	–
		Ampl.	6·6	3·9	11·8	–
	b	Lat.	88·0	13·0	81·0	–
		Ampl.	23·0	13·0	33·0	–
	c	Lat.	108·0	13·0	101·0	–
		Ampl.	27·2	2·9	38·5	–

* eg. P2a ampl = P2a – P2b amplitude

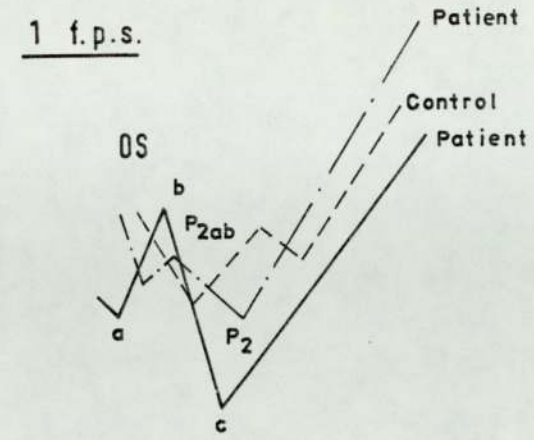
Fig. 6.10. Occipital Spike and P_{2ab} components at 1, 7 and 9 f.p.s. in Photosensitive patients, before Sodium Valproate treatment, and Normal Controls.

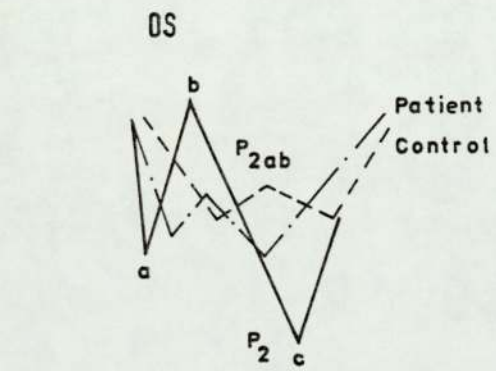
Of the 14 patients at 7 f.p.s., 4 had occipital spikes (mean latency, 92.75 msec.), and 3 patients possessed a P2ab component at the base (N = 2) or on the descending arm(N = 1) of P2 (mean latency of b, 104msec.). None of the control patients showed this component but one female subject, aged 13 years 10 months, exhibited an occipital spike of 84 msec. latency at 7 f.p.s. and 81 msec. at 9 f.p.s.. At these flash rates the occipital spike was equivalent to the N2 component and was related to the N2 latency at 1 f.p.s. (83 msec.). Of the 6 photosensitive patients recorded at 9 f.p.s.,occipital spikes were evident in 2 cases.

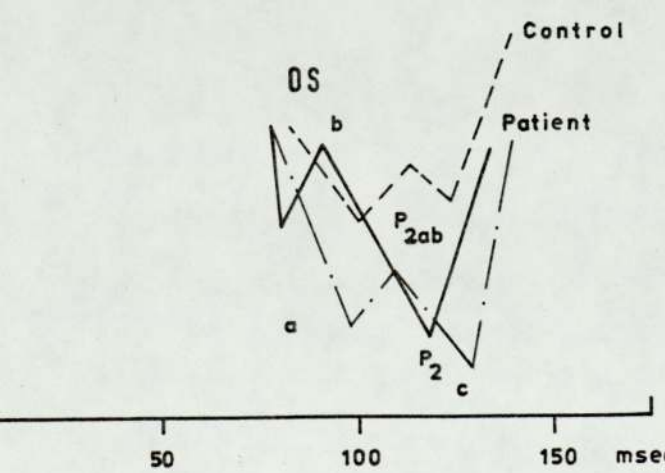
At optimum dosage, 3 out of 21 patients had occipital spikes at 1 f.p.s. (mean latency, 88 msec.) and a triphasic P2 wave occurred in 4 patients either on the descending arm (N = 2), base of P2 (N = 1), or ascending arm (N = 1). The mean latency of the small negative polarity was 93 msec.. This component was evident in 2 control subjects, on the positive and negative going wave of P2 respectively, but with a longer mean latency of 113.5 msec..

Occipital spikes were now present in the VEP and EEG of 7 out of 20 patients recorded at 7 f.p.s. at optimum dosage (mean latency 94.63 msec.). Three other patients, two of whom had not reached a significant improvement in photosensitivity and one patient, where evoked potentials were only recordable up to 5 f.p.s., also had occipital spikes. This means that the overall incidence of occipital spikes was 50%, a frequency similar to that determined for non-treated photosensitives from the EEG during routine testing of the sensitivity range (see Section 7.13). At 7 f.p.s., 2 patients had P2ab waves (mean latency 98 msec.) on the descending and ascending arm of P2 respectively. A similar occurrence was

Optimum Dosage







			Patient		Control	
			$\bar{x}$	S.D	$\bar{x}$	S.D.
P_2	a	Lat.	84 · 0	10 · 7	98 · 5	1 · 5
	*	Ampl.	3 · 3	2 · 7	8 · 6	2 · 9
	b	Lat.	93 · 0	13 · 5	113 · 5	3 · 5
		Ampl.	6 · 3	1 · 9	3 · 0	0
	c	Lat.	109 · 5	11 · 4	124 · 5	2 · 5
		Ampl.	29 · 9	18 · 1	15 · 8	1 · 8
OS	a	Lat.	78 · 3	6 · 8	–	–
		Ampl.	10 · 8	4 · 4	–	–
	b	Lat.	88 · 0	3 · 7	–	–
		Ampl.	20 · 4	3 · 3	–	–
	c	Lat.	104 · 3	5 · 4	–	–
		Ampl.	27 · 3	9 · 8	–	–
P_2	a	Lat.	91 · 0	12 · 0	102 · 0	1 · 0
		Ampl.	4 · 4	3 · 6	3 · 8	2 · 8
	b	Lat.	98 · 0	15 · 0	113 · 0	5 · 0
		Ampl.	6 · 1	0 · 3	2 · 6	0 · 1
	c	Lat.	113 · 0	14 · 0	130 · 1	2 · 5
		Ampl.	14 · 1	0 · 2	18 · 6	2 · 4
OS	a	Lat.	83 · 9	8 · 4	–	–
		Ampl.	16 · 4	7 · 6	–	–
	b	Lat.	94 · 6	8 · 1	–	–
		Ampl	25 · 7	14 · 2	–	–
	c	Lat.	122 · 0	12 · 1	–	–
		Ampl.	23 · 9	8 · 8	–	–
P_2	a	Lat.	98 · 0	3 · 5	101 · 0	2 · 0
		Ampl.	4 · 7	2 · 4	6 · 0	1 · 5
	b	Lat.	108 · 8	5 · 3	112 · 5	5 · 5
		Ampl.	10 · 5	6 · 9	3 · 9	0 · 9
	c	Lat.	128 · 0	14 · 9	124 · 0	8 · 0
		Ampl.	24 · 0	11 · 8	(17 · 0	–)
OS	a	Lat.	81 · 3	5 · 9	–	–
		Ampl.	9 · 2	6 · 9	–	–
	b	Lat.	91 · 3	6 · 3	–	–
		Ampl.	20 · 4	11 · 0	–	–
	c	Lat.	118 · 1	10 · 4	–	–
		Ampl.	19 · 5	10 · 2	–	–

* eg. P_{2a} Ampl. = P_{2a} – P_{2b} Amplitude

Fig. 6.11. The effect of Sodium Valproate on Occipital Spike and P_{2ab} components at 1, 7 and 9 f.p.s.

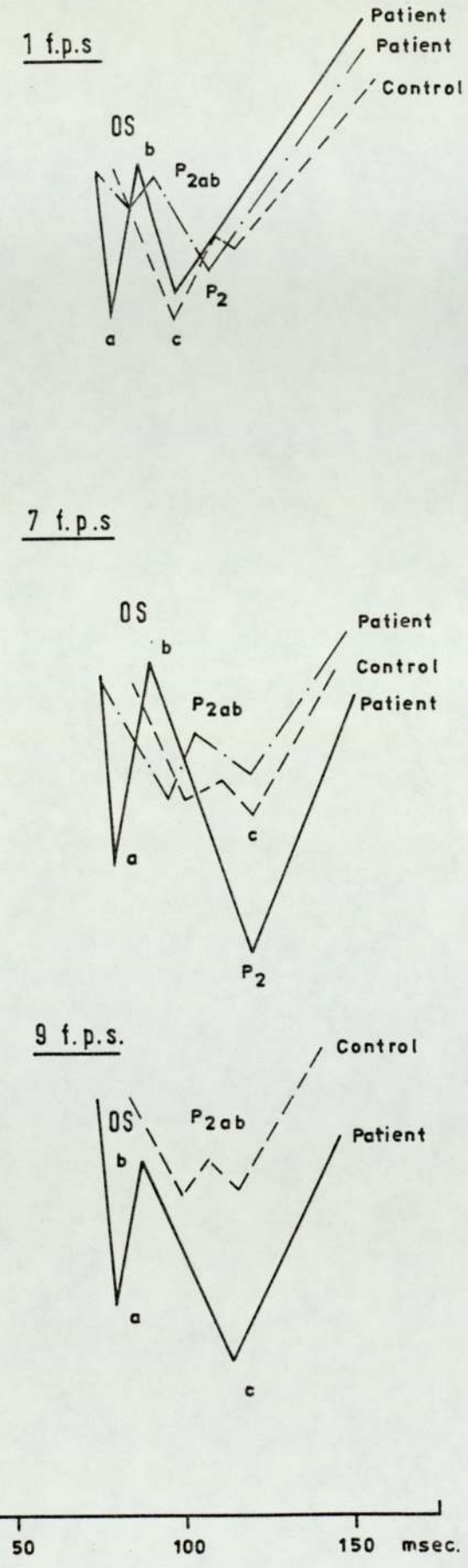
observed in 2 control subjects (mean latency 113 msec.). Out of 18 patients at 9 f.p.s., definite occipital spikes were present in the VEP of 7 patients. In another patient these spikes were evident in the EEG but, as the VEP was recorded using very short trains of flashes, no buildup of occipital spikes occurred,resulting in the absence of an occipital spike within the summated VEP. Three patients and two controls had triphasic P2 components which in the former occurred mostly on the positive going potential.

After withdrawal of sodium valproate, 1 patient had a definite occipital spike in her VEP at 1 f.p.s. (mean latency, 88 msec.) but as its negative going amplitude (20 μv.) was very similar to the amplitude of N2 (23 μv)., occipital spikes were not prominent in the EEG. Similarly, two other patients had sharp P2ab waves resembling small occipital spikes in the VEP, but which were non-apparent in the EEG. Two other patients had the usual type of triphasic P2 component occurring on the descending arm and at the base of P2.

At 7 f.p.s., 3 out of the 7 tested patients had occipital spikes in their VEPs and EEGs (mean latency 90.67 msec.). A triphasic P2 wave was present on the positive P2 deflection in 2 patients (mean latency, 108.5 msec.), and at the base of P2 in 2 control subjects (mean latency 112.0 msec.). Two of the 4 patients recorded at 9 f.p.s. had occipital spikes; none had P2ab waves. However, this component was evident in the VEP of 2 normal subjects near the base of P2 on the descending and ascending arm respectively.

Throughout the entire study, of the 10 patients with occipital spikes in the VEP, in only 3 cases was there definite evidence of the occipital spike 'growing out' of the triphasic P2 wave with increase in flash rate. Also, in 2

Post - Epilim



			Patient		Control	
			$\bar{X}$	S.D	$\bar{X}$	S.D.
P_2	a *	Lat.	85·0	7·8	98·0	–
		Ampl.	4·3	2·1	10·5	–
	b	Lat.	93·0	10·7	110·0	–
		Ampl.	11·7	4·5	1·5	–
	c	Lat.	108·0	13·6	117·0	–
		Ampl.	26·5	6·6	20·0	–
OS	a	Lat.	79·5	1·5	–	–
		Ampl.	17·9	2·4	–	–
	b	Lat	87·0	1·0	–	–
		Ampl.	15·5	6·5	–	–
	c	Lat.	99·0	1·0	–	–
		Ampl.	33·3	8·5	–	–
P_2	a	Lat.	96·5	13·5	101·0	1·0
		Ampl.	8·0	5·2	2·7	0·7
	b	Lat.	108·5	16·5	112·0	2·0
		Ampl.	5·1	3·7	4·3	2·8
	c	Lat.	120·0	10·0	121·5	0·5
		Ampl.	18·2	3·2	17·5	6·5
OS	a	Lat.	79·0	2·2	–	–
		Ampl.	25·1	8·6	–	–
	b	Lat.	90·7	0·5	–	–
		Ampl.	35·4	12·2	–	–
	c	Lat	120·0	6·4	–	–
		Ampl.	29·7	8·3	–	–
P_2	a	Lat	–	–	99·0	–
		Ampl.	–	–	4·5	–
	b	Lat.	–	–	107·0	–
		Ampl.	–	–	3·0	–
	c	Lat.	–	–	116·0	–
		Ampl.	–	–	17·0	–
OS	a	Lat.	80·0	2·0	–	–
		Ampl.	17·3	14·0	–	–
	b	Lat.	87·5	2·5	–	–
		Ampl.	24·4	11·2	–	–
	c	Lat.	114·0	11·0	–	–
		Ampl.	27·0	5·0	–	–

* eg. P_{2a} Ampl. = $P_{2a} - P_{2b}$ Amplitude

Fig. 6.12. Occipital Spike and P_{2ab} components at 1, 7 and 9 f.p.s after withdrawal of Sodium Valproate

patients it was the N2 component which clearly increased in amplitude, became sharper and took on the appearance of an occipital spike in the VEP and EEG. As mentioned, this effect was also observed in one female control subject at 7 and 9 f.p.s.. In another patient, when VEPs were compared at all flash rates and also with those of his paired control subject, it became evident that the occipital spike seen at 1, 7 and 9 f.p.s. was also the N2 component. Three other patients also showed occipital spikes in the VEP from 1 f.p.s.. In one patient where the occipital spike appeared initially at 7 f.p.s., and in 3 of the patients with spikes from 1 f.p.s., the negative potential of the occipital spike developed from the descending arm of P2 (N = 3) so that the final positive deflection (c) was in fact P2, or from the ascending arm of P2 (N = 1).

Comparison between patients and controls at 1 f.p.s. showed that significantly more patients (7 out of 25) than control subjects (4 out of 56) had a triphasic P2 component (χ^2 = 4.75 df 1, P = 0.025). However, at 7 and 9 f.p.s. there was no significant difference in the frequency of P2ab between patients (6 out of 20) and controls (8 out of 56), (χ^2 = 1.49 df1, P > 0.05). It is apparent, therefore, that although a triphasic P2 is an infrequent but normal finding in the evoked potential at faster frequencies, this component is more common in photosensitive patients and its incidence at 1 f.p.s. is significantly greater than usually seen in the normal population.

Further comparisons were made between the latency and amplitude of P2ab and the occipital spike. The first test involved these patients showing a P2ab wave at 1 f.p.s. and an

occipital spike at 7 f.p.s.. No significant difference was found in the latency of the first positive wave (a), the negative wave (b) and the amplitude of the negative going potential (a - b) between the triphasic P2 wave and occipital spike (Correlated t tests, $P > 0.05$). However, the amplitude of the occipital spike (b - c) was significantly greater at 7 f.p.s. than that of the P2b polarity at 1 f.p.s. ($t = 4.98$ df 3, $P = 0.01$). Also the latency of the second positive component (c) was significantly delayed in the occipital spike ($t = -3.63$ df 3, $P = 0.025$) as a result of its increased amplitude and longer duration. Lack of significance in the a-b amplitudes was probably due to the occurrence of more P2ab waves on the ascending arm of P2 than of occipital spikes.

The second test for determining a relationship between the two components was between patients with a triphasic P2 at 7 f.p.s., which had not developed into a spike, and those with an occipital spike (Independent t tests). The triphasic P2 had a significantly longer latency of the first positive deflection (a) ($t = 2.16$ df 12, $P = 0.05$) and was of a smaller amplitude (a - b) than the occipital spike ($t = - 2.54$ df12, $P = 0.025$). The negative polarity (b), although not differing significantly in latency ($t = 1.67$ df 12, $P > 0.05$), was of significantly greater amplitude (b - c) in the occipital spike ($t = - 2.99$ df 12, $P = 0.01$). As regards the second positive wave (c), no significant difference was found between the P2ab component and occipital spike at 7 f.p.s. for latency and amplitude (c - N3), ($t = 0.05$ and $- 1.77$ respectively df 12, $P > 0.05$).

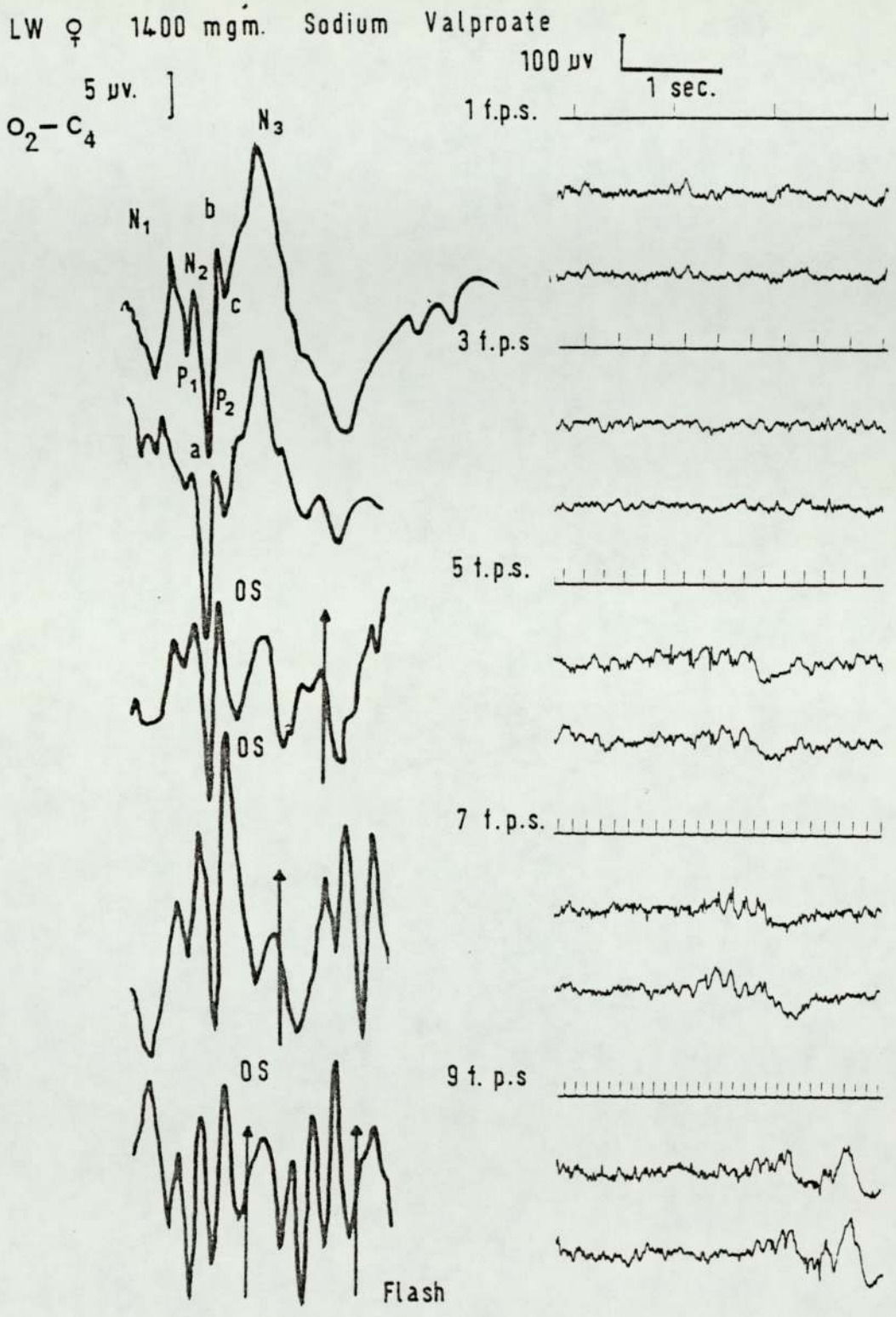


Fig.6.13. Occipital Spikes seen in the VEP and EEG at 5,7 and 9 f.p.s. develop from the P2ab component at 1 and 3 f.p.s.

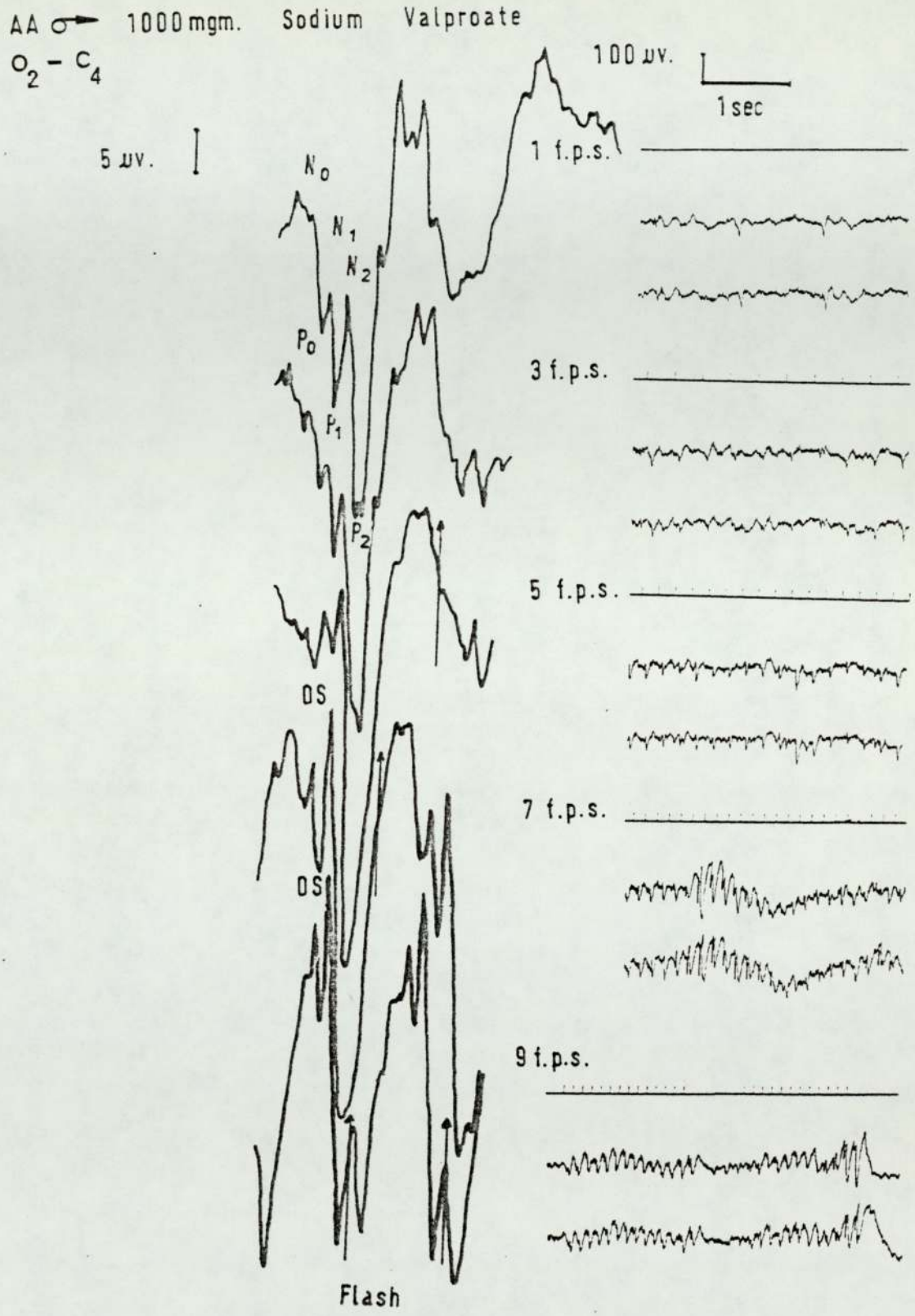


Fig. 6.14. Enhanced amplitude of N2 component develops into an Occipital Spike at 5, 7 and 9 f.p.s. (VEP at 9 f.p.s recorded in short intermittent runs of flashes.)

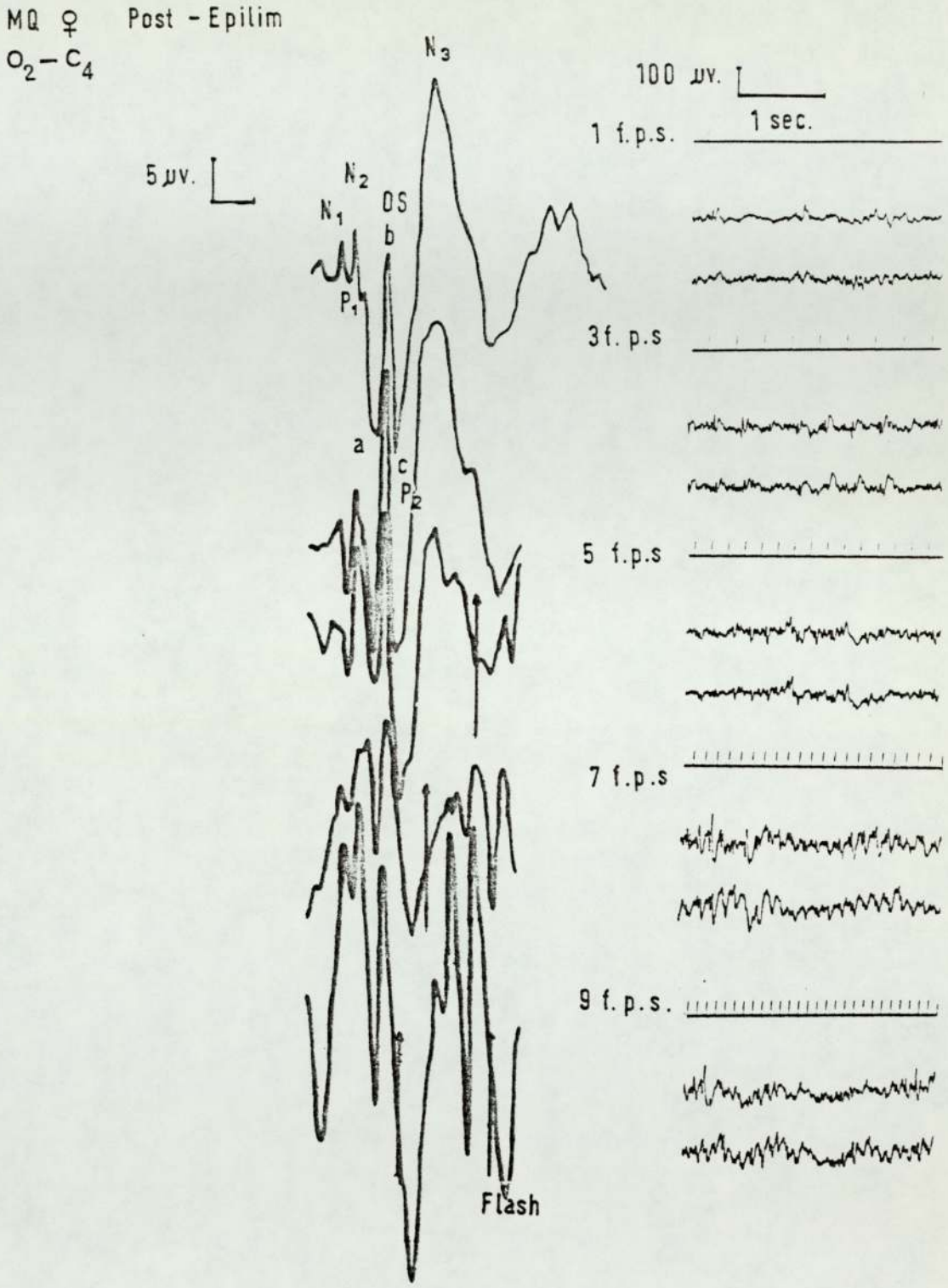


Fig. 6.15. Occipital Spikes seen in the EEG from 3 – 9 f.p.s. are also obvious on the descending arm of P_2 from 1 f.p.s.

Therefore, even when the occipital spike does not develop from a triphasic P2 a close relationship exists between latencies. However, the occipital spike at 7 f.p.s. may be of longer duration than the P2ab component at 1 f.p.s. in the same patient, and tends to occur earlier than the P2ab wave seen in other patients at 7 f.p.s.

The effect of sodium valproate treatment was tested at 1 and 7 f.p.s.. At both frequencies, there were no significant differences for the latency or amplitude of any component of the P2ab wave or the occipital spike at optimum dosage, or after withdrawal of sodium valproate in relation to pre-drug findings, or in the post-drug VEP in relation to optimum dosage (Correlated t tests, $P > 0.05$). This was confirmed in 4 patients with occipital spikes at 7 f.p.s. who had undergone all stages of treatment. A randomised block design test between pre-drug, optimum dosage, and the post-drug VEP showed that the latency and amplitude of the first positive wave and negative component of the occipital spike were not significantly affected by sodium valproate even though a marked improvement had occurred in the photosensitive EEG.

In conclusion, only one normal control (1.8%) showed an occipital spike, whereas in photosensitive patients the frequency of occipital spikes seen in the VEP was 50%. This is a much lower incidence than previously reported by Panayiotopoulos et al. (1972) as 87%, and Dimitrakoudi et al. (1973) as 91%, even though a similarly provocative stimulus was used for recording the VEP. The latter authors also found that 56.5% of patients had occipital spikes at 1 f.p.s., whereas in the present study this was only observed in 16% of photosensitives.

It is possible that in the absence of comparisons with normal controls, the large amplitude N2 component might be mistaken for an occipital spike. In 3 patients the occipital spike was the result of a definite enhancement at the N2 component, which is in disagreement with the above authors.

These previous authors did note, however, that the occipital spike usually developed from the descending arm of P2 and, in a few subjects, could be seen to 'grow out' of the triphasic P2 component with increasing flash rate. These observations are confirmed in the present study although, out of 7 cases with a P2ab component at 1 f.p.s., in only 3 cases was the occipital spike at 7 and 9 f.p.s. the result of P2ab augmentation. However, an overall relationship was found between the triphasic P2 wave and the occipital spike, particularly in the latency of the negative polarity. Both types of component were commonly seen on the descending (positive going) arm or at the base of P2. The triphasic P2 component was shown to be an infrequent but normal occurrence in controls (unlike the occipital spike) at 7 and 9 f.p.s.. However, this component was more common in the photosensitives and its incidence significantly greater at 1 f.p.s..

Sodium valproate treatment had no effect on the latency or amplitude of the triphasic P2 wave or the occipital spike.

7. TREATMENT OF PHOTOSENSITIVITY WITH SODIUM VALPROATE

7.1. Photic Stimulation Techniques.

All EEGs were recorded under standard conditions. At each investigation the patient was encouraged to relax and co-operate so that IPS would be given in a consistent manner. The level of background illumination, type of photo-stimulator and stimulus were all kept constant. A Grass PS22 stroboscope was used at either intensity setting 1 (1,058 Cd/m^2 or nits) or intensity 2 (1,363 nits). Prior to sodium valproate therapy, some patients were more photo-sensitive at the lower intensity due to a tendency to half-close their eyes with the brighter stimulus. Therefore, during subsequent treatment, investigations were conducted using the most provocative stimulus intensity seen in the untreated individual.

During recording the patient lay in a supine position in a dimly lit room of 4.6 nits background illumination, and was instructed to view the centre of the lamp placed 31 cms from the patient's eyes. This allowed the person to focus comfortably onto the stimulus as well as enabling easy monitoring of any eye movements. Jeavons et al. (1972b) recommended the routine use of a grid pattern for enhancing the efficiency of IPS as compared to a simple plain or diffused flash. In order to present a maximally provocative IPS, a fine black-lined grid patterns (Normatone HN 560) of square subtense 26' visual angle was superimposed on the diffused blue-white flash of 10 µsec. duration. It should be noted that the transmitted light intensity using the grid pattern was 40% of the plain diffused flash. Due to the lamp dimensions the overall circular light stimulus subtended 24°.

According to the neural representation equation of Drasdo (1977), a concentric stimulus field of this size stimulates exactly 75% of the brain's visual information channel capacity, total receptive fields or striate area.

The EEG was recorded on a 12-channel S.L.E. machine using a paper speed of 30 cm/sec, an overall time constant of 0.3 secs, 100 μv/cm. gain and high frequency filters only when absolutely necessary so that high frequency spike abnormalities would not go undetected. EEG activity was investigated using the 10/20 system (Jasper 1958) using a modified parasaggital montage (Fig. 6.4.). One channel of the EEG monitored the flash rate. The majority of patients are most sensitive with eyes-open than with eyes-closed (Jeavons and Harding 1975). Although in the present study testing was made under both conditions, all patients followed this trend and so the eyes-open results were analysed throughout the drug-trial.

7.1.1. Determination of the sensitivity range .

In determining the sensitivity range and its upper and lower limits for each patient, a 2-second train of flashes was given at every test frequency. The flash rate began at 1 f.p.s. and then in steps of two up to around 20 f.p.s. or until a flash rate was obtained which consistently evoked a PCR (i.e. at least twice). This became the lower limit. The frequency was then switched to maximum (60 f.p.s.) and decreased in steps of five until a PCR occurred. The flash rate was successively increased then decreased until the exact upper limit was determined, which again consistently produced a PCR. The sensitivity range was obtained by subtracting the lower limit (e.g. 10 f.p.s.) from the upper limit (e.g. 40

f.p.s.) and adding one, thus indicating the exact number of inclusive flash frequencies to which the patient was sensitive (e.g. 31).

Where distinct islands of sensitivity occurred, producing a divided range of critical frequencies, the sensitivity range was defined by the addition of the two sub-ranges, e.g. 10-20 f.p.s. and 40-50 f.p.s., which gives an overall range of 22 f.p.s.. The lower and upper limits still remained as the overall minimum and maximum frequencies; in the above example, 10 and 50 f.p.s..

7.1.2. Effect of intensity.

It has already been mentioned that patients were investigated throughout the study using either Grass intensity 1 or 2 depending on their pre-treatment EEG results. As the alteration in the sensitivity range and its limits was the main criterion during therapy, it was determined whether these intensities had any differential effect on the change in the photosensitive parameters. Before treatment 27 patients received two pre-drug EEGs. At both recordings 9 had been tested at intensity 1 and 10 at intensity 2. No significant difference was found in the alteration of the lower limit ($t = 0.53$ df17, $P > 0.05$) or in the alteration of the upper limit ($t = 1.15$ df 15, $P > 0.05$) between the two intensities. Therefore, as long as the lower or higher intensity was used consistently for each individual's drug-trial, which was most effective in the untreated condition, then overall treatment results would be comparable.

7.2. Behaviour of the Sensitivity Range prior to Therapy.

During the period from 1973-1977, 50 photosensitive patients received sodium valproate (Epilim) and were studied before receiving the drug, during drug therapy and, in 16 cases, following the withdrawal of medication. Of the 50 patients, 27 received two pre-drug (pre-Epilim) EEGs. The reliability study (see Section 5.1) has shown that there is no significant difference in the sensitivity range and its limits between repeat EEGs within a 3-month period. However, of the 27 patients, 10 were repeated within 3 months, 2 within 6 months, 5 within 1 year, 2 within 2 years and one at 2 years 2 months (mean time interval 5.78 months, S.D. 6.27 months). As a further control these patients were sex and age matched to patients not intended for sodium valproate therapy but who had also undergone repeat EEGs after the same period of time. The control patients were drawn from the 167 patients used in the prognosis study and in the majority of cases it was also possible to control for the clinical photosensitive history (i.e. Groups I, II and III).

The mean age of the 27 pre-drug patients was 14 years 5 months (S.D. 4 years 3 months) and that of control patients 14 years 2 months (S.D. 4 years 1 month). Correlated t tests were performed between the two groups for the variation in the lower limit, upper limit and the sensitivity range obtained at the repeat EEG investigation :-

Lower Limit	t = -0.45	df26	P > 0.05
Upper Limit	t = 0.41	df24	P > 0.05
Sensitivity Range	t = 0.30	df24	P > 0.05

There was no significant difference between the pre-drug patients and their matched controls on any parameter; neither was there any significant difference in the numbers showing improvement or deterioration in the sensitivity range of the groups ($\chi^2 = 0, P > 0.05$). It was concluded, therefore, that no spontaneous improvement of photosensitivity had occurred in the 27 patients prior to sodium valproate treatment.

It was also shown in the reliability study that standard anticonvulsants had no beneficial effect on the photosensitive response. In the 27 patients who were investigated twice before sodium valproate therapy, 16 were taking the same anticonvulsant at both pre-drug EEGs ('stable treatment'), 8 patients were on no medication ('no treatment'), and 3 patients had been taken off their drugs before the second EEG recording ('changed treatment'). An independent t test between the degree of improvement or deterioration in the sensitivity range between the 'no treatment' and 'stable treatment' patients was not significant at the 5% probability level ($t = 0.25$ df 21). This verifies the previous findings and confirms that drug treatment before sodium valproate had not improved these photosensitive epileptics.

7.2.1. Determination of a significance level.

The two pre-drug sensitivity ranges determined in the patients prior to sodium valproate therapy were compared to determine a percentage improvement in the sensitivity range which would correspond to a significant level of improvement. This was defined as the 95th percentile. When the direction of change in the sensitivity range was

taken into account, the mean percentage alteration was a reduction (i.e. improvement) of 9.3% with a standard deviation of 41.96%. For a Z score of 1.645 (95th percentile), the improvement in sensitivity had to be equal to or greater than 78% to be significant. Only one patient with a narrow sensitivity range (29 f.p.s.) at the the first pre-drug EEG (P1) showed such a spontaneous improvement between the two pre-treatment EEGs .
The 78% improvement level was therefore the criterion adopted during subsequent treatment with sodium valproate.

7.3. EEG Responses.

The EEG responses obtained during IPS were classified according to Jeavons and Harding (1975) depending on their distribution and morphology. PMRs were not seen in any of the patients as a high intensity light was not given during the eyes-closed testing. The sensitivity range described those frequencies which evoked a PCR. Responses were considered as PCRs when they resembled any of the categories described in Section 2.2.2., i.e. bilateral generalised typical or atypical spike and wave, polyspikes, polyspike and wave or slow wave discharges. As sodium valproate treatment progressed, it became necessary to describe degraded forms of PCRs. These were classified as follows :-

(i) Localised spike and wave/theta spike and wave/spikes or slow waves that are bilaterally symmetrical or asymmetrical but without frontal irradiation, e.g occipital theta spike and wave, occipital spikes;

(ii) On-, off- or mid-responses, i.e. non-persistent abnormality usually with frontal irradiation occurring at onset, offset or within the train of flashes. Single spikes are ignored unless associated with clinical change, viz. myoclonic jerks;

(iii) Exaggerated VEP with or without spikes, e.g. occipital on- and off-responses.

The exact lower limit, upper limit and frequency range that produced photic driving responses were

also determined. Responses were classified according to the occurrence of fundamental, harmonic or sub-harmonic driving.

7.4. Distribution of Improvement.

Of the 50 photosensitive patients who were treated with sodium valproate, 31 were female and 19 were male, ranging from 6 years 2 months to 29 years 9 months at the beginning of the therapy. All patients received at least one pre-drug EEG. As sodium valproate was introduced, other anticonvulsants were gradually withdrawn in 18 patients. However, 11 patients continued on reduced dosages of their previous drugs during the study. Five patients were taking ethosuximide, 4 patients phenobarbitone, 3 phenytoin and another acetazolamide. One patient received 10 mgm.of imipramine each night for enuresis. Overall, 8 patients were only taking one extra drug in addition to sodium valproate and 3 patients retained two extra drugs. Twenty-one patients were not taking other anti-convulsants one month before or during sodium valproate therapy. This drug was administered as described in Section 6.2..

The effect of sodium valproate on the sensitivity range was determined according to the criteria established at the pre-drug EEGs, and patients were divided into three 'effect' groups. The response to therapy was rated as 'cure' if there was complete abolition of photosensitivity, 'improved' if the sensitivity range was reduced by more than 78% and 'no significant improvement' if the reduction in the sensitivity range was less than 78%. Twenty-seven patients were 'cured', 12 were 'improved' and 11 showed no marked benefit from sodium valproate therapy (Fig. 7.1.). There was a significant difference between the number of patients who definitely improved and those who did not ($X^2 = 15.68$, df1, $P < 0.0005$).

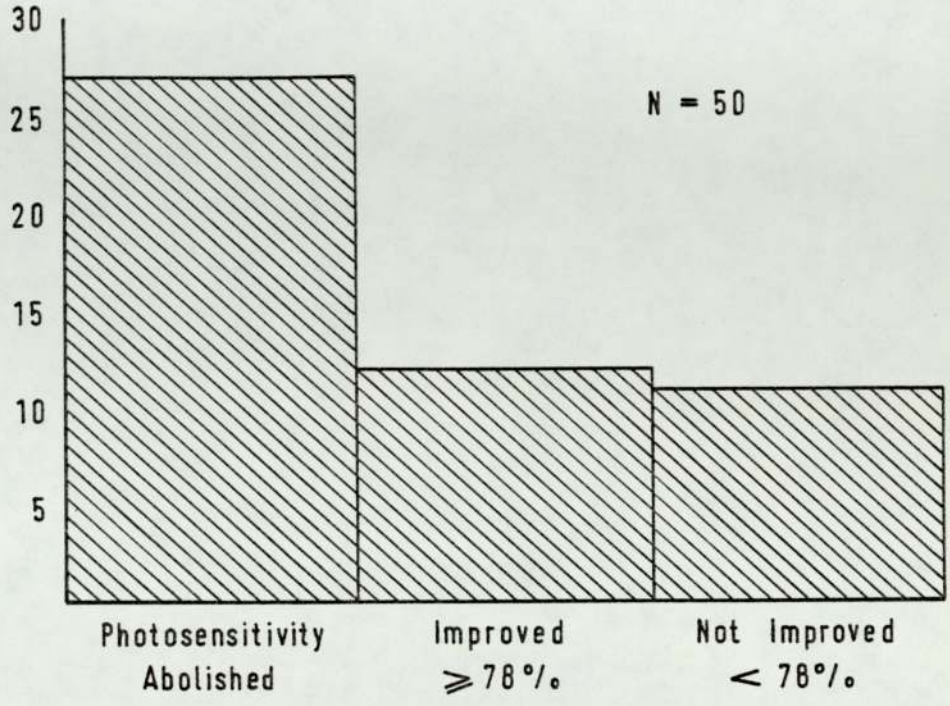


Fig. 7.1. The effect of Sodium Valproate therapy on the Photosensitivity Range.

A comparison between the number of patients on sodium valproate alone and those on other drugs achieving significant and non-significant improvement showed no marked difference (χ^2 = 0.57, df1, P > 0.05). Therefore, the presence of other drugs had no significant influence on patients attaining considerable improvement of photosensitivity.

It became obvious, therefore, that sodium valproate was efficacious in these patients. As a further test, the 50 patients were compared to untreated age, sex, and where possible clinically matched control patients. The time period between the last pre-drug EEG and that showing the best response to sodium valproate over the shortest interval (optimum dosage EEG) ranged from 1 month to 2 years 9 months (mean, 9.34 months, S.D. 8.07 months). At optimum dosage the mean age of the 50 treated patients was 15 years 6 months (S.D. 4 years 10 months). Correlated t tests and χ^2 2 x 2 contingency tables (Table 7.1.) show that compared to untreated patients the improvements in the sensitivity range and both its upper and lower limit are highly significant in the sodium valproate treated group.

Similar results were obtained for all parameters when only the 39 patients on sodium valproate alone at optimum dosage were compared with their matched controls (P = 0.0005).

Test	Lower Limit		Upper Limit		Sensitivity Range	
	Treated	Un-Treated	Treated	Un-Treated	Treated	Un-Treated
Mean Alteration f.p.s.	+ 8·89	0·04	- 34·36	- 0·73	-28·24	- 0·11
S.D.	7·20	4·48	18·13	8·55	18·61	9·28
t	5·51		10·11		7·47	
df	46		44		44	
P *	P = 0·0005		P = 0·0005		P = 0·0005	
No. Improved	45	24	48	21	48	22
No. N/C or Deteriorated	4	23	1	25	1	24
χ^2	17·76		30·08		28·22	
df	1		1		1	
P *	P = 0·0005		P = 0·0005		P = 0·0005	

Table 7.1. Comparison of the Sensitivity Range and its Limits in Sodium Valproate treated Photosensitive patients with untreated control patients

(* All tests are 1 tailed; N/C = no change)

7.5. Dosage.

Within the 50 patients, sodium valproate dosage ranged from 600 - 1600 mgm daily. The patient on 600 mgm. was a young girl (7 years 6 months) who was the sibling of a photosensitive epileptic in the group. She herself had no clinical history of fits but was being treated for her photosensitivity as seen with laboratory IPS. A female on 1600 mgm. (17 years 8 months) was overweight and, although eventually showing 85% improvement at this optimum dosage, was suspected of being incompliant in taking the tablets. Overall, 26 patients were receiving 1000 mgm, 12 patients 1200 mgm, 9 patients 800 mgm. and 1 patient was on 1400 mgm. daily at optimum dosage. A series of independent t tests between those patients who were cured or significantly improved and those with non-significant improvement showed no differences in the actual daily dosage (mgm) of sodium valproate ($P > 0.05$).

However, when dose was related to bodyweight, a significant relationship became obvious (Table 7.2.). Such measurement was available on 24 patients. Only one patient, who obtained abolition of photosensitivity, was taking another drug - namely imipramine 10 mgm. at night for enuresis, besides 1200 mg/day of sodium valproate. In those patients cured or significantly improved, the mean daily dosage was 23.62 (S.D. 6.74) mg/kg which was significantly higher ($t = 1.87$, df22, $P = 0.05$) than in the unsuccessful patients (mean 17.41, S.D. 4.32 mg/kg). However, the difference in duration of treatment between these two groups was non-significant ($t = 0.74$, df 48, $P > 0.05$) even when only the cured patients were compared to the unsuccessfully treated group ($t = 0.63$. df36. $P > 0.05$). Similarly there was no significant difference between the ages of the improved

and unimproved patients ($t = -1.29$, df 48, $P > 0.05$).

Fig. 7. 2. shows dosage (mg/kg.) plotted against age. As age increases, the ratio of sodium valproate to body weight falls ($r = -0.72$). Hence quite a wide dose ratio (16.13 - 38.46) mg/kg/day is effective in significantly reducing photosensitivity and achieving full control. Many authors quote 20-30 mg/kg. as effective sodium valproate dosage for seizure control in children (Fau and Garrel 1968; Dumon-Radermecker 1969; Reckitt and Coleman 1973), although others have used up to 80 mg/kg. in chronic epileptic cases (Olive et al. 1969, Barnes and Barot 1975; Haigh and Forsyth 1975). Adults are generally dosed according to age and not weight, between 1000-1600 mg/day (see Section 4.5.). From Fig. 7.2. it can be seen that for 14 children up to 15 years old the effective dosage ranged from 17.35 to 38.46 mg/kg/day, 7 children being within the 20-30 mg/kg. range. Of the 5 patients over 15 years, 3 were taking 1000 mgm., 1 was taking 1200 mgm. and another received 1600 mg/day. It appears, therefore, that in this sample effective dosages of sodium valproate in the treatment of photosensitivity were within the generally reported therapeutic range for seizure control.

	Cured or Improved >78%	Not Improved < 78 %	Significance Level *
No. of patients	39	11	P = 0·0005
Clinical Groups I	16	6	Non – sig.
II	12	4	
III	9	1	
Male / Female	14 / 25	5 / 6	Non – sig.
Sodium Valproate Dosage mg / kg.	23 · 62	17 · 41	P = 0 · 05
Mean Duration of Treatment	9 · 36 months	7 · 56 months	Non – sig.
Mean Age	15 years 3 months	17 years 3 months	Non – sig.

(* All tests 1-tailed)

Table 7.2. The effect of Sodium Valproate on the Photosensitivity of 50 patients.

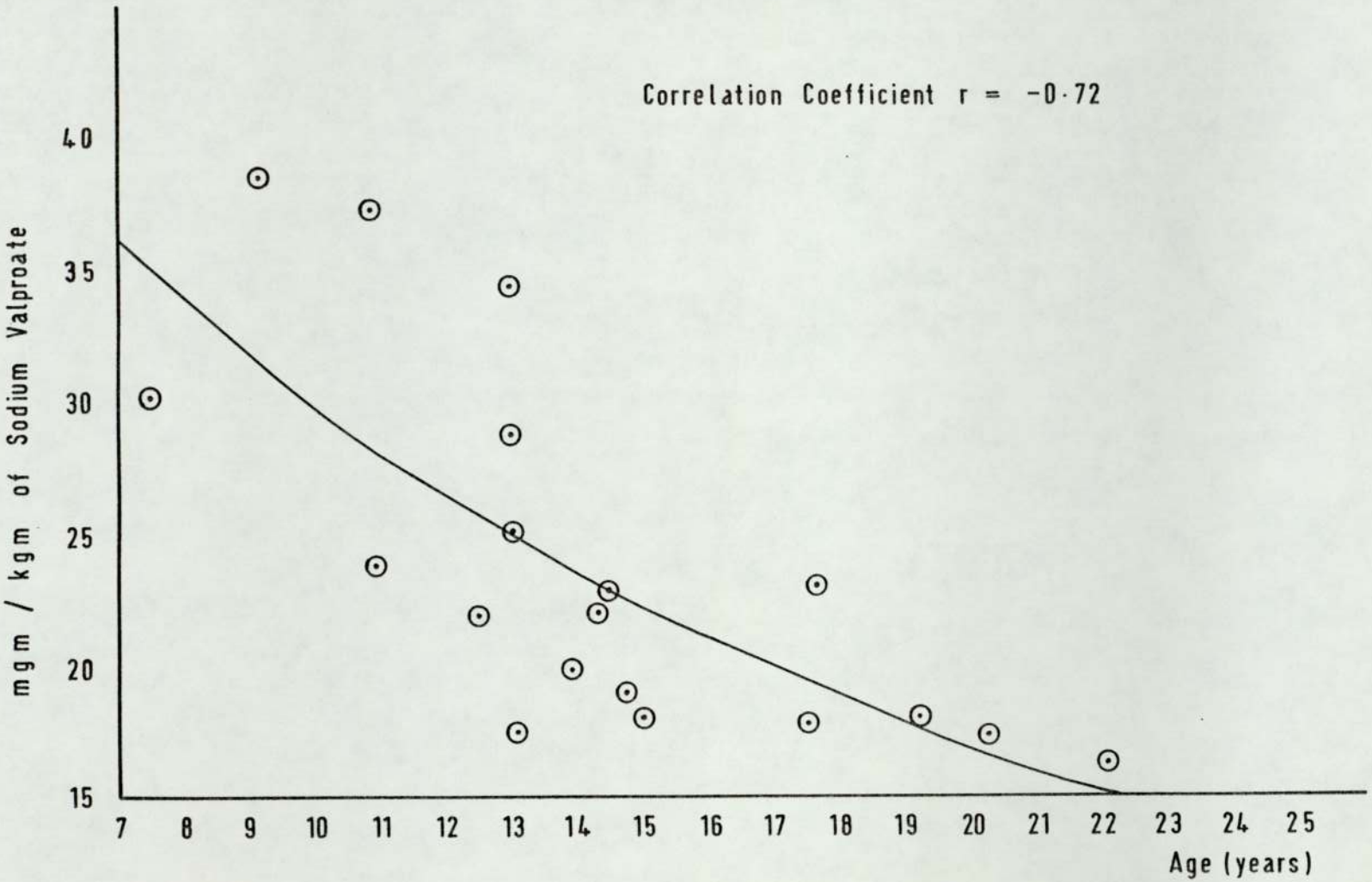


Fig. 7.2. Variation in dosage according to age for significant improvement in Photosensitivity.

7.6. Dosage Effects on Photosensitivity Parameters.

As duration of treatment , age effects and actual dosage showed no significant difference between the improved and unimproved patients, whereas dosage in relation to body-weight was significantly greater in the former group, this indicates that patients have a somewhat idiosyncratic buildup to that level. Series of correlated t tests were conducted for the upper and lower limits and the sensitivity range to see if there was any appreciable change in these parameters at the various dose levels (mg/day) of sodium valproate in relation to those measured prior to therapy.

In patients who were increased from 800 to 1000 mgm. (N = 22) of sodium valproate, there was no significant alteration in the lower limit although more patients showed an improvement at 1000 mgm. (χ^2 = 3.2, df1, P = 0.05). Conversely a significant degree of improvement occurred at the upper limit which was reflected in the sensitivity range (see Table 7. 3.), but there was no significant difference in the numbers of patients improving at 800 and 1000 mgm. (χ^2 = 0, df1, P > 0.05). Similar results were obtained for 17 of these patients who were taking sodium valproate alone at both dose levels. The remaining 5 patients were also receiving reduced dosages of other anticonvulsants.

It was apparent, therefore, that the general trend of improvement in the sensitivity range seen at 800 mgm. was a real effect which increased at 1000 mgm.. This was due to the particular responsiveness of the upper limit with the higher dose of sodium valproate which resulted in an increasing insensitivity at fast flash rates. However, although the actual magnitude of change in the lower limit was similar at

800 and 1000 mgm. when compared to pre-drug levels, movement of the lower limit towards a relatively higher flash rate (i.e. improvement) occurred in more patients at 1000 mgm..

The same pattern was seen for the sensitivity range and both its limits between 800 mgm. and 1200 mgm. (N = 12). Any improvement in these parameters at the higher dose level between 1000 and 1200 mgm. (N = 17), 1200 and 1400 mgm. (N = 5) and 1000 and 1400 mgm. (N = 5) (Table 7.3.) failed to reach significance for all patients, and for those who were receiving sodium valproate alone, without additional anticonvulsants. In conclusion the most dramatic effect on the sensitivity range occurs up to 1200 mgm, significant effects still being seen after 800 mgm. After 1200 mgm, any changes occur more gradually and, in the majority , additional benefit is slight. The overall reduction in photosensitivity seems mainly due to the lowering of the upper limit so that insensitivity is primarily seen at the higher flash frequencies. The responsiveness of the lower limit is slower, although the number of patients showing gradual improvement increases with increase in dosage.

	DOSE	Mean Alteration	S.D.	DOSE	Mean Alteration	S.D.	Significance
Lower Limit	P_2 - 800	+ 5·46	6·96	P_2 - 1000	+ 10·10	9·39	N.S.
	P_2 - 800	+ 6·31	8·47	P_2 - 1200	+ 4·92	4·81	N.S.
	P_2 - 1000	+ 7·53	8·91	P_2 - 1200	+ 6·21	5·00	N.S.
	P_2 - 1000	+ 3·80	4·31	P_2 - 1400	+ 7·60	3·50	N.S.
	P_2 - 1200	+ 7·00	6·48	P_2 - 1400	+ 7·60	3·50	N.S.
Upper Limit	P_2 - 800	- 19·96	19·55	P_2 - 1000	- 28·17	23·09	P = 0·05
	P_2 - 800	- 12·77	12·38	P_2 - 1200	- 27·38	25·17	P = 0·005
	P_2 - 1000	- 15·06	22·15	P_2 - 1200	- 26·06	23·53	N.S.
	P_2 - 1000	- 19·80	20·82	P_2 - 1400	- 37·00	16·19	N.S.
	P_2 - 1200	- 27·0	19·95	P_2 - 1400	- 37·00	16·19	N.S.
Sensitivity Range	P_2 - 800	- 19·32	18·42	P_2 - 1000	- 26·20	19·08	P = 0·05
	P_2 - 800	- 17·62	12·93	P_2 - 1200	- 27·85	20·23	P = 0·025
	P_2 - 1000	- 19·00	20·26	P_2 - 1200	- 26·00	19·18	N. S
	P_2 - 1000	- 16·80	17·85	P_2 - 1400	- 30·60	17·73	N. S.
	P_2 - 1200	- 27·20	16·70	P_2 - 1400	- 30·60	17·73	N.S

Table 7.3. Alteration of the Sensitivity Range and its Limits at successive dosage increases of Sodium Valproate.

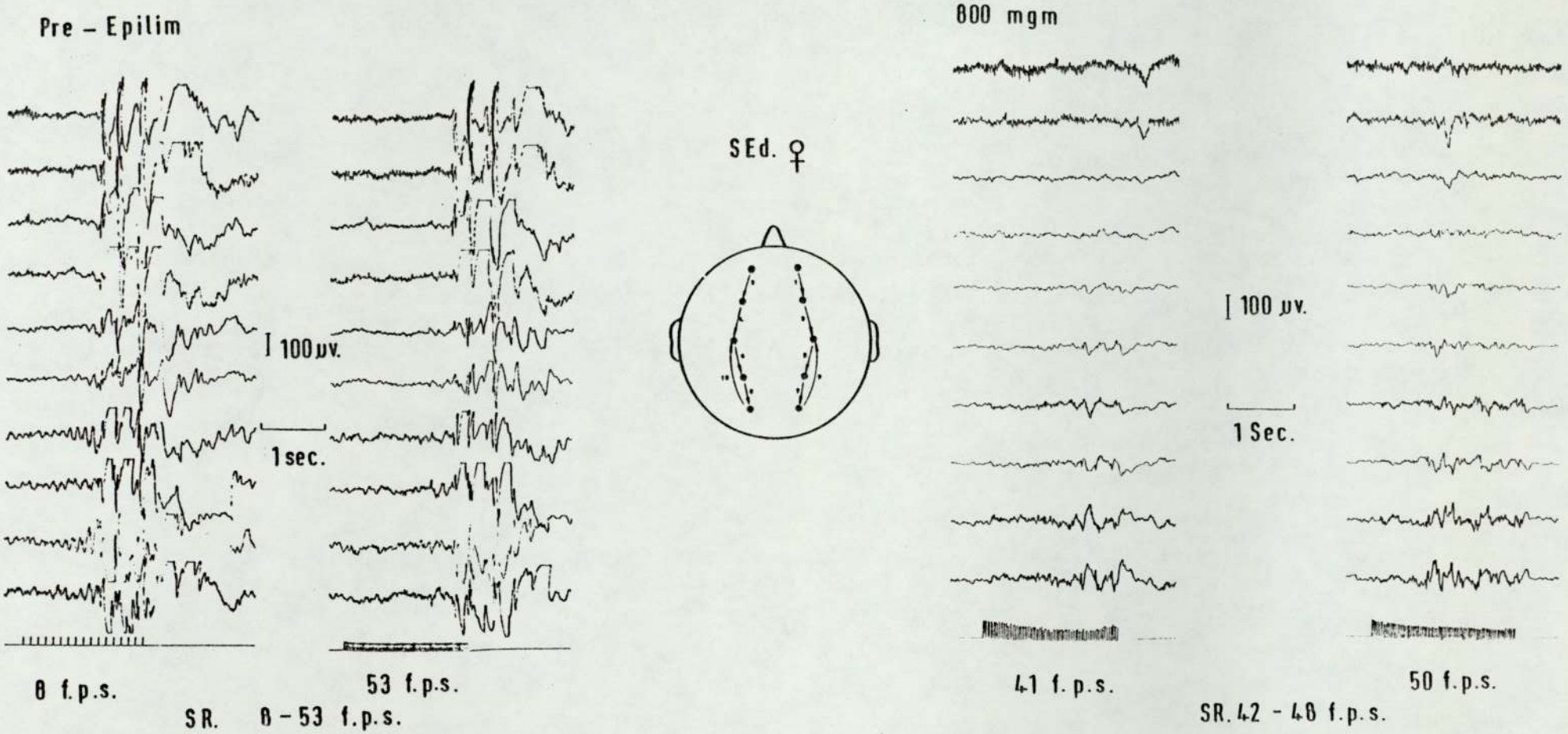


Fig. 7.3.1. The effect of Sodium Valproate dosage on the Sensitivity Range (SR) Prior to treatment the Sensitivity Range of SEd. was 8 – 53 f.p.s., with Occipital Spike triggering of the PCR at the Lower Limit. At 800 mgm. daily the SR had reduced to 42 - 48 f.p.s. with Degraded Responses at 41 and 49 - 50 f.p.s.

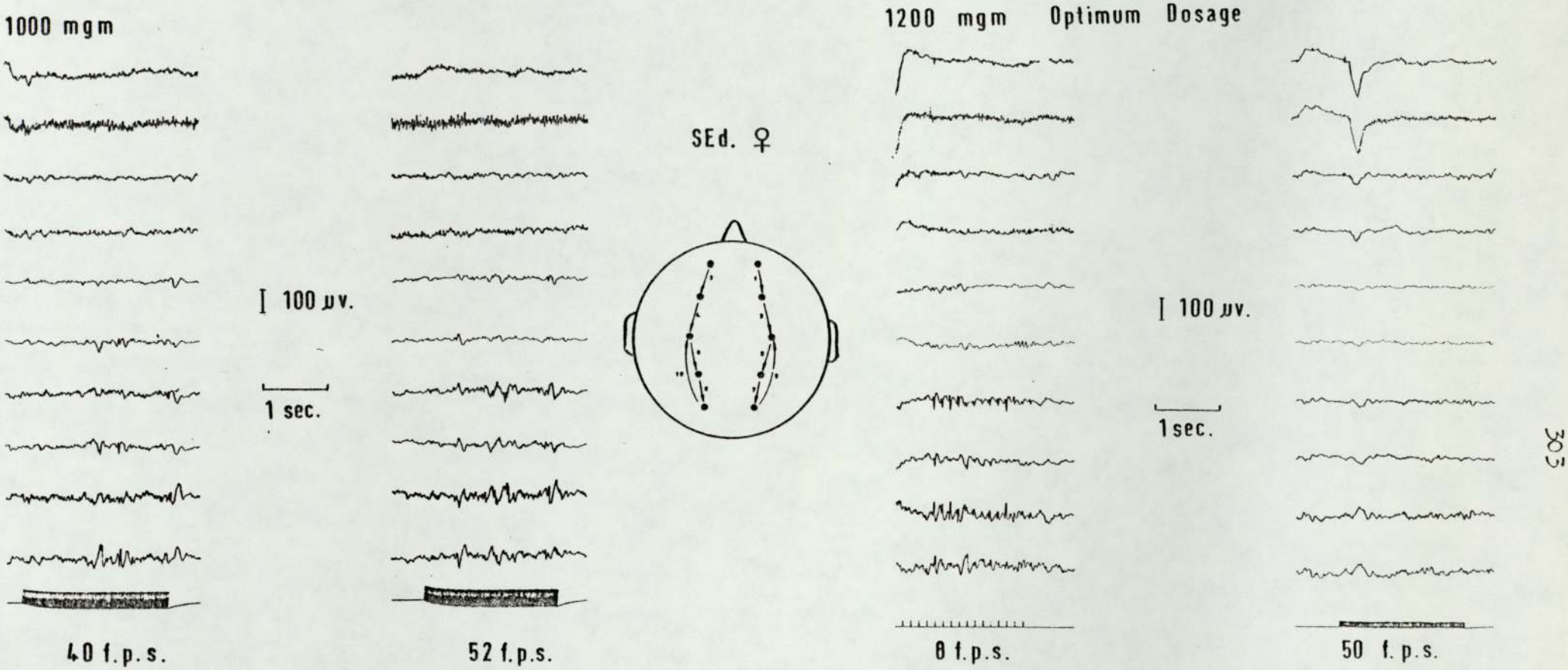


Fig. 7,3,2. The effect of Sodium Valproate dosage on the Sensitivity Range (SR.) At 1000 mgm. IPS evoked no PCRs but Degraded Responses (theta spike and wave) occurred between 40 - 52 f.p.s. Total abolition of Photosensitivity was seen in this patient at 1200 mgm daily. Following Occipital Spikes persisted at low flash rates.

7.7. Cures.

The 50 sodium valproate treated patients were compared to the entire prognosis group of 167 photosensitive patients. Over the years 19 of these latter patients showed a spontaneous cure of photosensitivity, whereas abolition of photosensitivity resulted in 27 of the treated patients. This difference was highly significant (χ^2 = 39.34, df1, P = 0.0005). Of the 27 cured patients receiving sodium valproate, 16 were on 1000 mgm, 5 on 1200 mgm, 4 on 800 mgm, 1 on 1400 mgm and the prophylactic patient only required 600 mg/day. The mean time interval between the last pre-drug EEG and the first treatment EEG showing total disappearance of the PCR was 9.36 months (S.D. 7.92 months). On the other hand, spontaneous abolition in the untreated patients had required an average duration of 2 years 9 months (S.D. 2 years 10 months) from the first photosensitive EEG referral. This time period was significantly longer than that taken for sodium valproate to exert a cure (t = 3.4, df44, P = 0.005).

Patients' ages in the two groups were similar (t = 0.08, df44, P > 0.05). The mean age of the cured, treated patients was 14 years 8 months (S.D. 4 years 1 month), and that of cured prognosis patients 14 years 9 months (S.D. 4 years 3 months). There was no significant difference, either, in the proportion of males and females between the two groups. Nine males and 18 females were cured on sodium valproate; 7 males and 12 females achieved a spontaneous cure (χ^2 = 0.005, df1, P > 0.05).

In the entire group of 50 treated patients, the ratio of Group 1 (photosensitive only) to Group II (flicker sensitive plus spontaneous fits) was 131:100 and of Group I to Group III (spontaneous fits only) 191:100. However, when

considering only the 27 cured patients, these ratios became 217:100. In the 19 spontaneous cure prognosis patients, the Group I to Group II ratio was 100:200 and Group I to Group III, 100:300. It was found that the difference between clinical groups was significant (χ^2 = 4.18, df 1, P = 0.025) as more of Group I than Group II and III showed complete abolition of photosensitivity when treated with sodium valproate than in the prognosis patients. This indicates that in the purely photosensitive epileptic patient the likelihood of total cure is far greater with sodium valproate therapy.

No significant difference was observed between the treated and untreated cured patients as regards a concomitant normalisation of the basic record, from an originally non-specific or truly abnormal EEG, and those who retained these abnormalities in the resting record despite the disappearance of PCRs (Fisher-Yates Contingency test P > 0.05). Therefore, a normal basic EEG was equally certain to accompany abolition of photosensitivity through sodium valproate treatment as that cured spontaneously.

7.8. Withdrawal of Sodium Valproate.

Sixteen of the 50 photosensitive patients were withdrawn from therapy after receiving sodium valproate for varying periods. Ten patients received the drug for more than 1 year, 1 patient for 12 months, 1 for 11 months and 3 were dropped from the trial either due to non-compliance or side effects of vomiting. One female patient was treated prophylactically for 2 months only, (see Table 7.4.). There were 9 females and 7 males and all were compared to sex, age and clinically grouped matched controls who had received no sodium valproate therapy, but had an equivalent time interval between their repeat EEGs.

Eleven of the 16 patients receiving treatment were no longer photosensitive at their optimum dose level. Of these 11 patients, 7 were taking 1000 mgm, one 800 mgm, one 1200 mgm and one 1400 mg/day of sodium valproate. The prophylactic patient received no more than 600 mg/day. Two other patients showed a less than 55% reduction in sensitivity and 2 patients achieved a significant reduction of more than 78% of their pre-treatment sensitivity ranges.

At optimum dose level, the mean age of these 16 patients was 13 years 7 months (S.D. 3 years 5 months) and the time interval between this EEG and the last pre-drug EEG (pre-Epilim 2, P2) ranged from 1 month to 1 year, 11 months (mean 8.4 months, S.D. 6.84 months). When compared to matched control patients, significantly more of the sodium valproate treated patients showed an improvement in both the lower and upper limit and the sensitivity range (Fisher-Yates Contingency tests, $P = 0.005$ respectively). Also the degree of improvement in all these parameters was significantly greater

Initials	Sex	Clinical Group	Age yr/mth.	Epilim mgm.	% Imp R *	Time Interval from P_2	Duration of Therapy	Post-Epilim % S.R. *	Duration off Epilim
A A	M	2	16/2	1000	35	0/1	0/1	1) 97 2) 115	0/2 0/4
KBr	M	1	13/0	1200	100	1/3	2/0	80	0/2
JC	F	2	22/1	1000	100	0/6	1/1	1) 115 2) 108	0/2 0/5
MCI	M	3	11/6	1200	79	0/5	0/5	173	0/7
JD	M	1	10/11	800	100	0/1	0/10	1) 123 2) 118	0/3 0/5
JE	F	1	16/9	1000	0	1/1	1/1	206	0/2
HJ	F	3	11/3	1000	100	0/9	2/1	1) 77 2) 31 3) 15	0/1 0/4 0/11
RH	M	2	14/5	1200	81	0/6	2/2	57	0/4
SMi	M	1	9/2	1000	100	0/10	2/2	79	0/1
DQ	M	1	10/5	1000	100	1/8	1/10	1) 0 2) 0 3) 3	0/1 0/3 0/7
MQ	F	2	14/9	1000	100	1/11	2/4	1) 2 2) 53 3) 90	0/1 0/5 0/10
SR	F	1	12/6	1000	100	0/6	1/6	102	0/1
PSa	F	1	16/7	1000	100	0/1	0/11	10	0/1
PSI	F	No Fits	7/6	600	100	0/2	0/2	1) 250 2) 400	0/5 0/8
LW	F	1	15/0	1400	100	1/3	1/9	1) 325 2) 150 3) 325	0/2 0/4 0/6
RW	F	1	15/1	800	53	0/1	1/0	1) 0 2) 324 3) 271	0/3 0/7 1/1

Table 7.4. Withdrawal of Sodium Valproate in 16 patients

* Improvement at Optimum Dosage (Imp^R.) and alteration in the Post-drug Sensitivity Range (S.R.) is expressed as a % of the Pre-drug S.R.

than for the control patients (Table 7.5.1.). Fig. 7.4. shows the distribution of improvement in the sensitivity range over the treatment period.

Prior to withdrawal, 11 of the 16 patients had a further EEG after reaching an optimum dosage of sodium valproate. However, one patient reduced his own dosage from 1200 to 1000 mg/day (RH) and another (RW) had been increased from 800 to 1200 mg/day but without further improvement. Parameters were therefore established for the 9 stabilised dosage patients at the last treatment EEG. Any alteration in the sensitivity range and its limits between optimum dosage and the last treatment EEG was non- significant (Table 7.5.2.). In fact, when compared to untreated control patients, significantly more sodium valproate treated patients had undergone absolutely no change in all parameters (Fisher-Yates Contingency tests, P = 0.025 respectively).

Comparison was made between the last-treatment EEG and pre-drug photosensitivity levels. The mean time interval between these two EEG investigations was 1 year 9 months (S.D. = 5.76 months). Table 7.5.1. shows that after prolonged treatment with sodium valproate, there is significant improvement in the sensitivity range and its limit in comparison to the changes seen in untreated patients after a similar time period. However, although both the upper limit and the sensitivity range showed a greater incidence of improvement in treated patients, the frequency of improvement in the lower limit was not significantly different from that seen in the untreated norm. The result was due to 2 out of the 9 treated patients who showed no discrepancy in their lower limit between their pre-drug and last treatment EEGs (i.e. relapse of the

Parameter	P_2 to Optimum Dosage v Controls	P_2 to Last - Treatment v Controls	P_2 to Post - drug v Controls	P_2 to Post - drug ($\leq$ 3 months) v Controls	P_2 to Post - drug ($>3 \leq 7$ months) v Controls
Lower Limit	t = 3·03 P = 0·005	t = 2·74 P = 0·025	t = 0·69 N.S.	t = 1·04 N.S.	t = − 0·45 N.S.
Upper Limit	t = 5·43 P = 0·0005	t = 2·84 P = 0·025	t = 1·41 N.S.	t = − 0·62 N.S.	t = 3·05 P = 0·01
Sensitivity Range	t = 5·28 P = 0·0005	t = 2·45 P = 0·025	t = 1·61 N.S.	t = − 0·59 N.S.	t = 1·05 N.S.
Sample Size	16	9	16	13	11
Mean Time Interval from Pre-drug EEG(P_2)	8·4 months (S.D. 6·84 months)	1year 9months (S.D. 5·76 months)	1year 7months (S.D. 8·04 months)	1year 6 months (S.D 6·84 months)	1year 8 months (S.D. 9·36 months)
Mean Withdrawal Period	—	—	3·12 months (S.D. 2·04 months)	1·85 months (S.D. 0·77 months)	5·36 months (S.D. 1·15 months)

Table 7.5.1. Alterations in the Sensitivity Range and its Limits during the treatment of 16 'Withdrawal patients'.

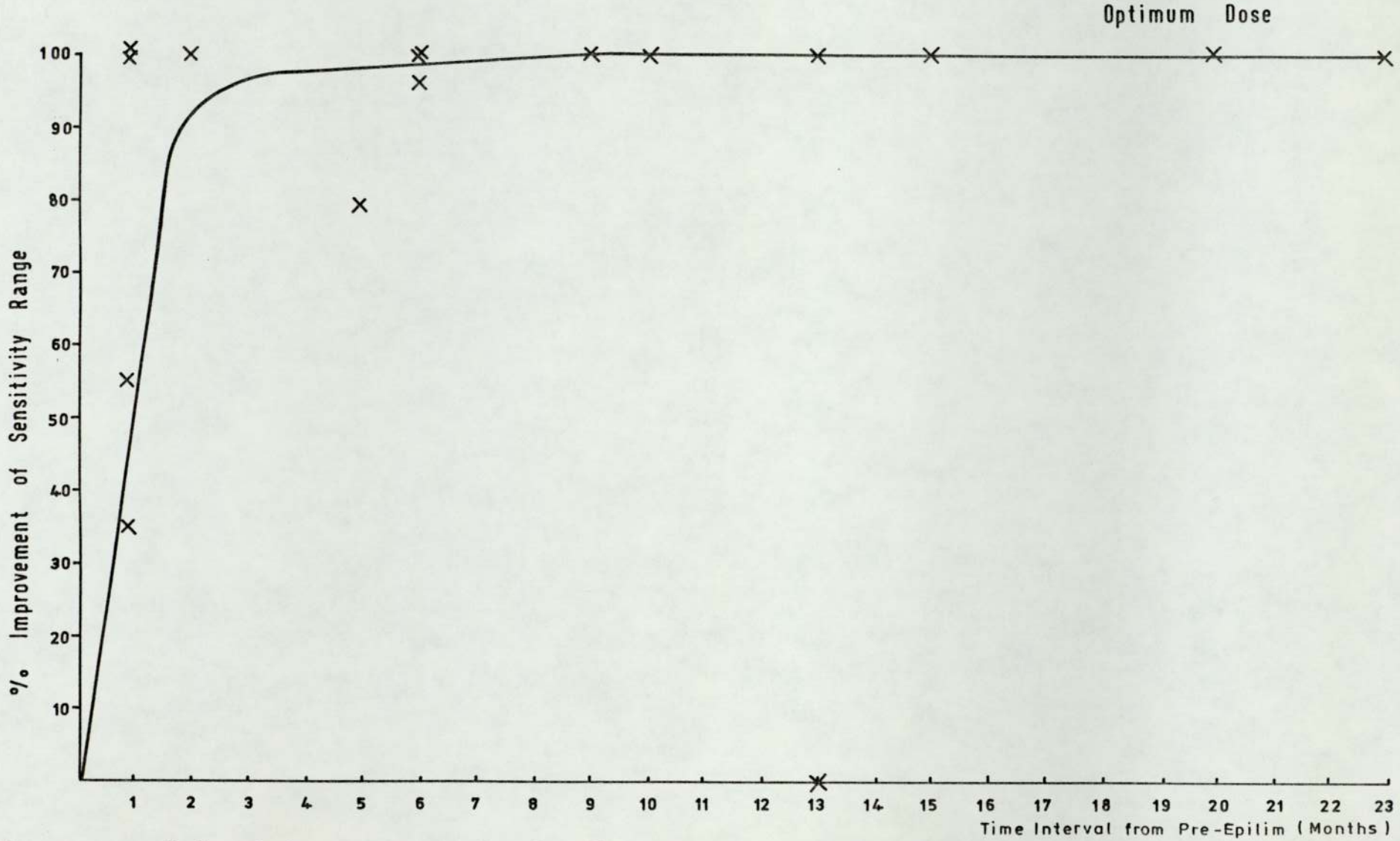


Fig. 7.4. Rate of Improvement in the Photosensitivity Range for 16 patients eventually withdrawn from Sodium Valproate

Parameter	Optimum Dosage to Last - Treatment v Controls	Last - Treatment to Post - drug v Controls	Last - Treatment to Post - drug (≤ 3 months) v Controls	Last - Treatment to Post - drug (> 3 ≤ 7 months) v Controls	≤ 3 months v 7 months Post - drug
Lower Limit	t = - 1·37 N.S.	t = 2·45 P = 0·025	t = 1·62 N.S.	t = 2·12 P = 0·05	t = - 0·39 N.S.
Upper Limit	t = 0·08 N.S.	t = 2·62 P = 0·025	t = 2·24 P = 0·025	t = 4·06 P = 0·005	t = - 2·14 P = 0·05
Sensitivity Range	t = - 0·91 N.S.	t = 2·19 P = 0·025	t = 1·83 P = 0·05	t = 1·80 N.S.	t = - 0·99 N.S.
Sample Size	9	13	11	9	7
Mean Time Interval Between EEGs	9·12 months (S.D. 4·56 months)	3·12 months (S.D. 2·04 months)	1·82 months (S.D. 0·72 months)	5·33 months (S.D. 1·05 months)	—
Mean Withdrawal Period	—	〃	〃	〃	—

Table 7.5.2. Alterations in the Sensitivity Range and its Limits during the treatment of 16 'Withdrawal patients'.

lower flash rate(s)) despite the fact that the other 7 patients showed an improvement. Also one of these improved patients (KBr) had achieved full control of photosensitivty at optimum dosage but 9 months later, at his last-treatment EEG although retaining some improvement in both sensitivity limits in comparison to pre-drug measures, now only showed a 44% (non-significant) improvement in the sensitivity range. It is interesting that these 3 patients who relapsed in photosensitivity, particularly at low flash rates, all had occipital spikes precipitating the PCR.

All 16 patients underwent at least one post treatment (post-Epilim) investigation within 7 months of the cessation of treatment. The mean time interval between the last treatment and the post-drug EEG was 3.12 months (S.D. 2.04 months). The general effect of terminating sodium valproate was either a reappearance of photosensitivity where this had been abolished or an increase in the photosensitivity that had remained during the treatment. Fisher-Yates Contingency tests for the sensitivity range and its limits showed a significantly greater frequency of deterioration ($P \leqslant 0.015$ respectively) after withdrawal of sodium valproate in comparison to the last treatment EEG than would normally be seen after this time interval. Table 7.5.2. shows that for all parameters the amount of this deterioration was significantly larger in the patients previously treated with sodium valproate than in matched control patients.

The sensitivity ranges recorded from each patient's most reactive post-drug EEG were compared to those obtained just before commencement of therapy (Fig. 7.5.). The three

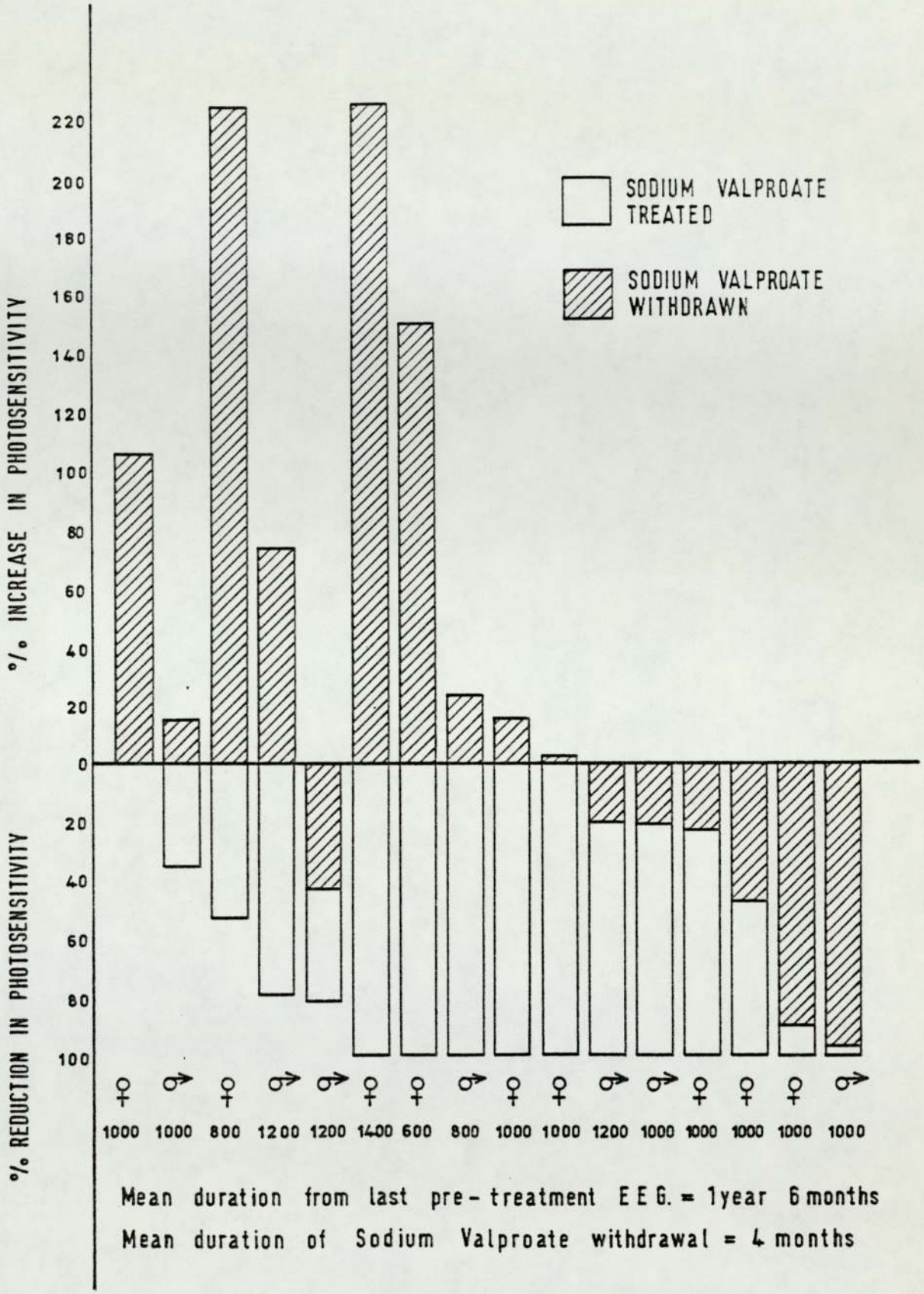


Fig. 7.5. Behaviour of the Photosensitivity Range during and after Sodium Valproate treatment in relation to pre-drug levels for 16 'Withdrawal Patients'.

female patients (RW, PSl, LW) showing at least a 150% deterioration in their ranges, previously had narrow ranges of 17, 5 and 4 flash frequencies respectively. Although there is a wide dispersion of the post-treatment sensitivity ranges as compared to pre-drug levels, neither the upper and lower limits nor the sensitivity range showed any significant difference in comparison to the alterations that occurred in a matched control group (Table 7.5.1.) over the same time period (mean 1 year 7 months, S.D. 8.04 months). There was also no significant difference between the numbers of treated and untreated patients as regards the direction of change in all parameters (Fisher-Yates Contingency tests $P > 0.05$). From these results, therefore, it appears that sodium valproate does not have any significant post-treatment, long-term effects on photosensitivity.

When post-drug follow-up EEGs were differentiated into those recorded within 3 months of withdrawal (N = 13) and after 3 months but up to 7 months (N = 11), similar results were obtained for alterations in the sensitivity range and both its limits for the 3-month period, as seen for the overall withdrawal findings (Table 7.5.1.). The alterations in the sensitivity range and the lower limit at 7 months also followed similar trends. However, at this later period the deterioration in the upper limit in relation to pre-drug findings was significantly greater than that normally observed.

It appears, therefore, that after 3 months the upper limit of sensitivity range had reached or surpassed its initial pre-treatment value. Within 3 months of withdrawal it is possible that the upper limit had not attained its

original level in some patients but, as upper limit pre-drug to post-drug comparisons were not reflected as significant alterations in the sensitivity range, a true long-term after-effect of sodium valproate is still doubtful. Fig.7.6.shows the behaviour of the sensitivity range after withdrawal of sodium valproate in relation to pre-treatment levels. As the period from withdrawal increases, the difference between the sensitivty range before and after therapy decreases and, in some patients, actually deteriorates. The relationship is weak, however, as seen by the small negative correlation ($r = -0.33$) between the two variables. Even so, up to 3 months after commencement of withdrawal of sodium valproate there is small clustering of still improved sensitivity ranges.

In order to investigate further the effects of withdrawal from treatment, the sensitivity range and both limits for the 3 month and 7 month period were compared to those obtained at the last occasion whilst receiving sodium valproate. Results were obtainable on 11 patients investigated within 3 months of withdrawal and on 9 patients investigated or re-investigated after 3 months but before 7 months (Table 7.5.2.). In both groups significantly more treated patients showed deterioration in all parameters after cessation of the drug compared to untreated control patients (Fisher Yates Contingency tests $P < 0.05$). However, whereas the sensitivity range at 3 months showed a greater degree of deterioration than is normally seen within this period, the alteration after 3 months was not significant.

It is obvious that at 3 months the deterioration in sensitivity range was attributable to that seen in the upper

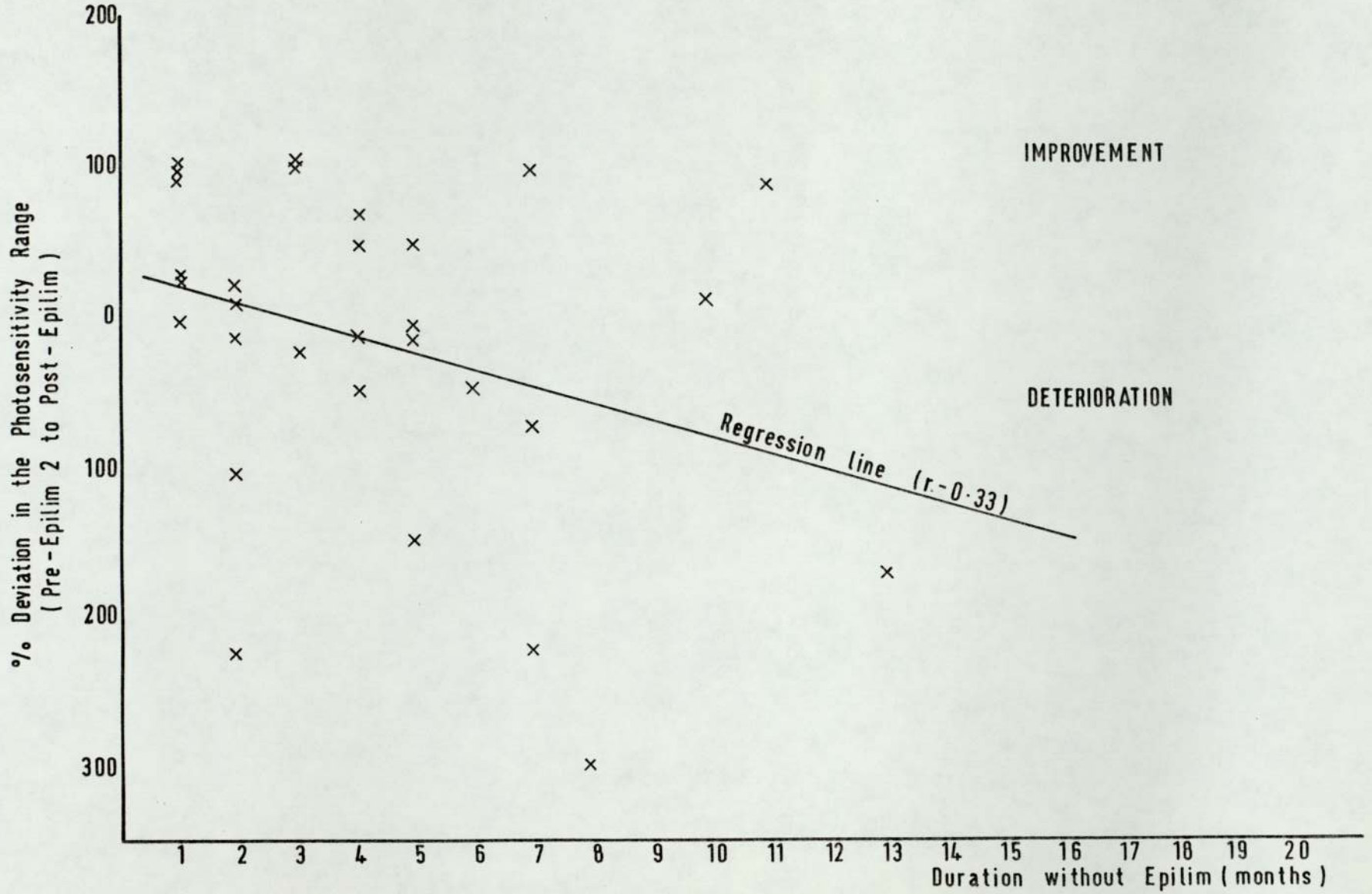


Fig. 7.6. Behaviour of the Photosensitivity Range after cessation of Epilim in comparison to Pre-Epilim Photosensitivity (N = 30 EEG's)

limit. However, although no marked change was seen in the lower limit, acquisition of only a few flash frequencies from a non-photosensitive state (e.g. 0 to 5 f.p.s.) would be needed for the re-establishment of a lower limit. Similarly, patients retaining their cured state would effectively show zero alteration and other patients, who previously had residual photosensitivity at their last treatment EEG (N = 5), now showing the usual deviation in flash rate would all contribute to this non-significant change in the lower limit. In the 7 month withdrawal group, one patient who had still been free from photosensitivity at 3 months now showed isolated sensitivity at 45 f.p.s. which meant that both his lower and upper limits had significantly altered by 45 flash frequencies. However, combination of a lower limit at high flash rates with an equally high upper limit would result in an apparent small alteration in the sensitivity range. Similarly, the same effect could result from a small change in a wider sensitivity range during the short time interval between two post-drug follow-up EEGs. Only 2 patients were actually receiving their first post-drug investigations at 5 and 7 months after withdrawal of sodium valproate.

Due to all these variables, further comparisons were made on the findings of 7 patients who underwent post-treatment EEGs within both time intervals. Alteration to the lower limit and sensitivity range prior to 3 months did not differ significantly from that seen after 3 months and up to 7 months (Table 7.5.2.). However, the upper limit showed a significant difference indicating that further deterioration had occurred after the 3-month period.

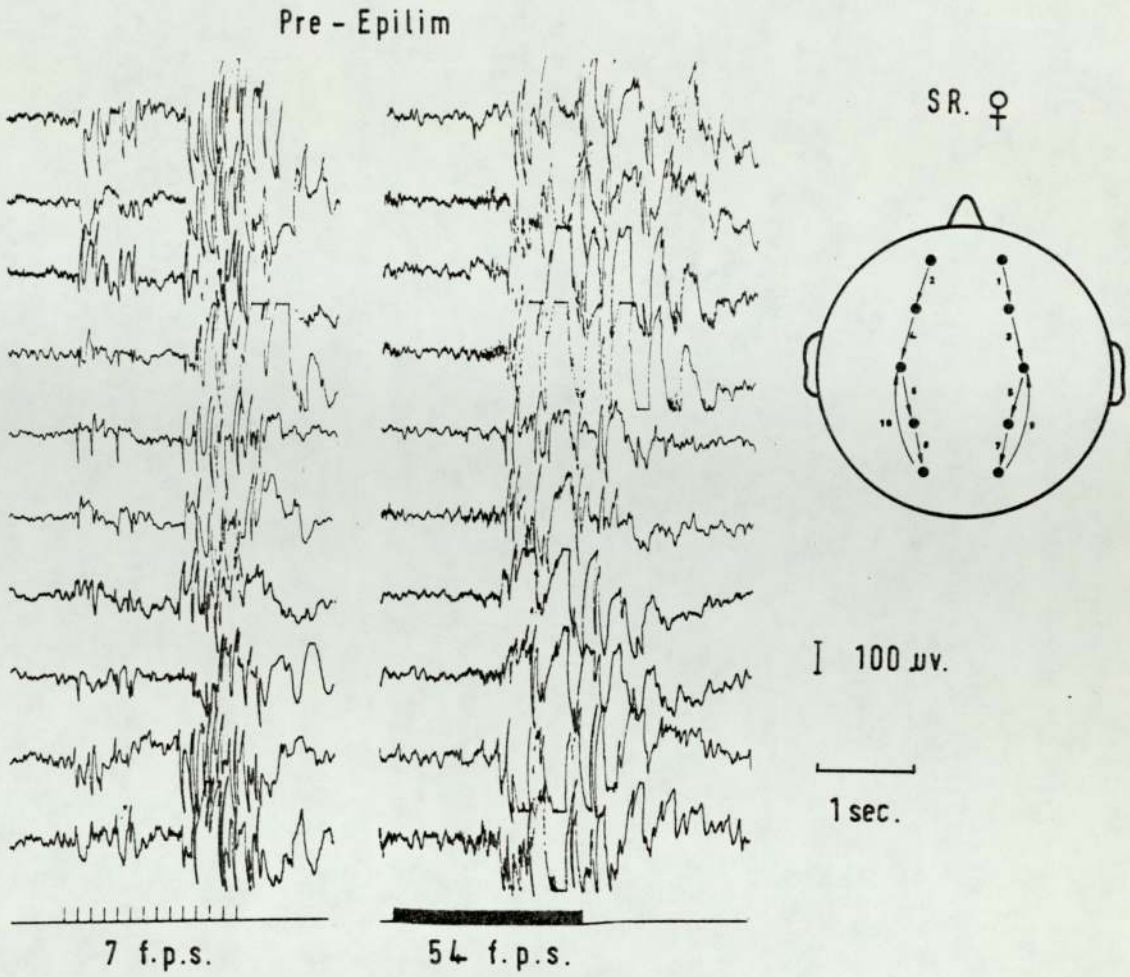


Fig. 7.7. Withdrawal of Sodium Valproate after 1 month causes a return of both the Lower and Upper Limits of the Sensitivity Range to Pre-drug levels.

It is concluded, therefore, that if sodium valproate therapy is withdrawn, patients generally return within 7 months to a degree of photosensitivity not signifantly different from that previously seen before treatment. There does, however, appear to be a continuing but gradually decreasing effect of the drug on the fast frequencies of the upper limit.

7.9. Sex Differences.

As shown in Table 7.2., 14 out of 19 males and 25 out of 31 females were significantly improved in photosensitivity when receiving sodium valproate. This difference was non-significant at the 5% probability level (χ^2 = 0.05, df 1). Similarly, no significant difference existed between the sexes when the 19 spontaneously cured, untreated prognosis patients were compared with the 27 patients who attained complete abolition of photosensitivity on sodium valproate therapy (χ^2 = 0.005, df1, P > 0.05).

There was no differential effect between males and females in the patients who were eventually withdrawn from sodium valproate as regards the proportion showing significant improvement during therapy, or deterioration after cessation of the drug in relation to pre-drug levels (Fisher-Yates Contingency tests P > 0.05 respectively).

Despite the overall lack of difference in effect between the sexes, the female patients who significantly or non-significantly improved at optimum dosage were re-classified according to the phase of their menstrual cycle (when known) at that particular EEG investigation. Due to the low numbers in each group, two major divisions of low oestrogen (i.e. pre-menstrual and menstrual phases N = 5, together with the 7 'no menarche' patients) and High Oestrogen (i.e. pre-ovulatory, ovulatory and luteal phases N = 6) were compared using the Fisher Exact probability test. No significant difference was found between the two groups as to the number of significantly improved female patients (P = 0.27). A similar result was obtained (P = 0.18) when the 'no menarche' patients were excluded from analysis.

In conclusion, there appears to be no obvious interaction between the sex hormones and the efficacy of sodium valproate.

7.10. Group Differences .

Analysis of sodium valproate cures (Section 7.7) showed that significantly more purely photosensitiive patients (Group 1) reached a total abolition of photosensitivity when receiving sodium valproate than normally occurs in the untreated patient population. Further tests were conducted to determine if the drug was more effective in treating photosensitivity within any particular clinical group.

Of the 50 photosensitive patients, 48 were classifiable into standard clinical groups (Table 7. 2.). As previously mentioned, one patient had no history of fits and was being prohpylactically treated. Another patient had a clinical history of syncope with no clear evidence of precipitation by flickering light. When considering those patients showing marked improvement in photosensitivity, no significant difference was found between the frequency within Group I, II or III (χ^2 = 2 df2, P > 0.05); neither was there any significant difference in the frequency of improvement or non-improvement between the purely photosensitive patients (Group I) and the spontaneous epileptics with or without additional fits triggered by flicker (Group II and Group III) (χ^2 =0.10 df1, P > 0.05).

It is apparent that although clinically flicker-sensitive patients stand a better chance of undergoing a complete cure when receiving sodium valproate than if left untreated, the drug possesses no differential effectiveness between the clinical groups.

7.11. Types of Abnormality.

Although the precise nature or duration of photically evoked abnormalities are not of diagnostic importance, such measurements may be of therapeutic value (Jeavons and Harding 1975). The EEG responses during IPS were analysed carefully in the 29 photosensitive patients consistently investigated at the Neuropsychology Unit, Aston University, throughout their drug trial. PCRs were classified as described in Section 2.2.2. and other types of degraded abnormality as described in Section 7.3.. Of the 29 patients, 27 underwent their last pre-drug EEG at the Neuropsychology Unit. The rank order of PCR type and percentage occurrence was as follows :-

(i) Polyspikes and slow waves of varying frequency, N = 22 (81.5%);

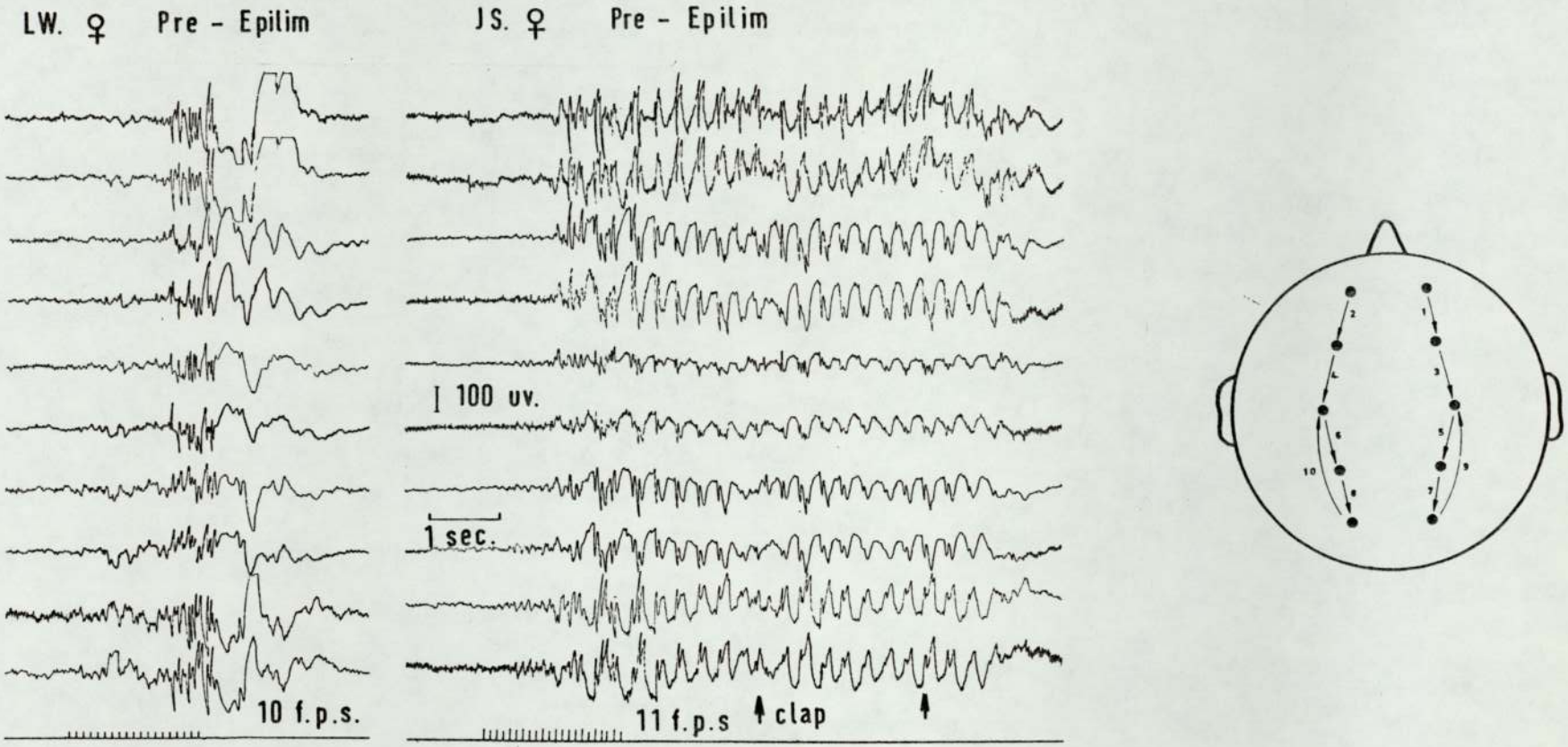
(ii) Atypical spike and wave, N = 12 (44.4%);

(iii) polyspikes, N = 5 (18.5%);

(iv) Generalised sharp waves and/or slow waves, N = 3 (11.1%);

(v) Typical spike and wave, N = 1 (3.7%).

In the 5 patients showing polyspike PCRs, 2 had associated myoclonic jerking of the limbs. Fourteen patients (52%) exhibited more than one type of PCR. Of these, 13 always showed a polyspike and slow wave PCR of varying frequency at some point during testing. The other varieties of PCR could occur separately or, even though the flash stimulus was always presented for a standard 2 seconds, could change morphology during this short stimulation period. It was concluded that if IPS was prolonged, it was possible for the PCR to change from polyspikes to polyspike and slow wave to atypical spike and wave to slow waves.



a) Polyspike and Slow Wave PCR.

b) Typical 3 c.p.s. Spike and Slow Wave PCR. with brief Absence

Fig. 7.8. Examples of two types of PCR. a) Polyspike and Slow Wave PCR was far more common than b) 3 c.p.s. Spike and Slow Wave PCR, with associated Absence.

Obviously not all patients' PCRs would necessarily begin with polyspikes and, in most untreated patients, prolonged IPS would terminate in a fit. Also patients with absence seizures would invariably show typical 3-4 c.p.s. spike and wave PCRs. However, the above sequence is intended to show that the slow wave component generally increased with flash duration. The pure slow wave response mainly appeared as an after-discharge at termination of the flash (6 patients in the sample.).

Besides the PCR, many patients showed degraded responses either in place of a PCR usually at frequencies outside the sensitivity range, or at times preceding the onset of the PCR. The rank order of degraded responses prior to sodium valproate treatment was :-

(i) Ill defined PCRs i.e. confined mainly to posterior derivations, poor frontal extension or non-persistent on-, off- or mid-responses, N = 18 (66.7%);

(ii) Occipital spikes, N = 15 (55.6%);

(iii) Occipital spike and wave, N = 14 (51.9%);

(iv) Occipital slow waves, N = 4 (14.8%);

(v) Non-persistent sharp waves and slow waves, N = 4 (14.8%);

(vi) Isolated sharp waves, N = 2 (7.4%).

The confounding effects of eye-blinks during IPS producing brief abnormalities occurred in 4 patients. Actual on- and/or off- responses were observed in 13 cases (48.2%). In the patients whose PCRs were at times preceded by degraded responses, no obvious difference was noted between the types of PCR that were preceded by degraded abnormality con-

taining occipital spikes (N = 14) and that not including occipital spikes (N = 12). Degraded responses were observed prior to polyspike and slow wave, atypical spike and wave and mixed PCRs. No degraded responses were seen before typical spike and wave or polyspike PCRs..

7.11.1. Dosage effects on abnormality.

Increase in sodium valproate dosage was accompanied by a decrease in PCR appearance but an increase in the incidence of degraded responses. Twelve of the 29 patients received 800 mgm. of sodium valproate daily. The most usual type of PCR was polyspikes and slow waves, seen in 9 patients (75%) followed by atypical spike and wave (N = 5, 41.7%) and then polyspikes (N = 4, 33.3%). Fifty per cent of the patients exhibited two types of these PCRs. All patients showed ill-defined PCRs as the sensitivity range limits became inconsistent. On- and off-responses occurred in 11 patients (91.7%) and occipital spikes were detected in 10 patients (83.3%).

Twenty-four patients received a dose of 1000 mg/day. Only 11 (46%) showed a definite PCR, which was either polyspike and wave seen in 8 patients (33.3%), atypical spike and wave in 5 patients (20.8%) and, in 1 patient, polyspikes (4.2%). In 5 other patients, all abnormality had completely disappeared and 8 more now showed only degraded responses during IPS, again the most common type being ill-defined PCRs (54.2%). On- and off-responses were fairly frequent (41.7%). Occipital spikes occurred in 50% and occipital spike and wave in 41.7% of patients. Eyeblinking was now less effective in evoking abnormality during IPS and was seen only once in 2 patients. At 1200 mgm. daily, the distribution of photically evoked responses in 13 patients was very similar to the pattern

seen at 1000 mgm. of sodium valproate.

The detailed EEG analysis of 13 patients after withdrawal of sodium valproate (mean 2.77 months, S.D. 1.76 months) showed a recurrence of PCRs in 12 patients and a retention of insensitivity in another. The distribution of responses was very similar to that seen at the pre-drug EEG; 12 patients possessed polyspike and slow wave PCRs (92.3%); 6 had atypical spike and wave (46.2%); polyspike discharge and sharp waves with or without slow wave complexes occurred in 2 patients (15.4%) respectively. However, in some cases, although the sensitivity range returned quantitatively, the critical flash frequencies tended to be a little more inconsistent when compared to pre-drug levels and degraded responses were common. Some inconsistency was expressed as on-, off- and mid-responses (N = 12, 93.3%) or ill-defined PCRs (N = 10, 76.9%). The frequency of occipital spiking remained essentially unchanged (N = 8, 61.5%) and was often accompanied by occipital theta waves.

7.11.2. Degraded responses and the sensitivity range.

At each dosage of sodium valproate, comparison was made between the range of frequencies evoking a true PCR and the frequencies at which degraded responses occurred. The difference between the lower limit of the actual sensitivity range and the lowest flash rate evoking a degraded response was significantly greater at 800 mgm. ($t = 3.68$, df21, $P = 0.005$) and 1000 mgm. ($t = 3.05$, df19, $P = 0.005$) than see at the last pre-drug EEG. The

difference between the upper limits of both response categories at 800 mgm. was non-significant when compared to pre-drug levels ($t = -1.69$, df19, $P > 0.05$). However, the difference reached significance ($t = -2.13$, df19, $P = 0.025$) at 1000 mgm. as the gap between the upper limit of the sensitivity range and that of the degraded responses became far wider at this dosage. The difference between the true sensitivity range and the range of frequencies evoking degraded abnormality was significantly smaller prior to treatment than at 800 mgm. ($t = -2.21$, df19, $P = 0.025$), 1000 mgm. ($t = -2.69$ df19, $P = 0.01$), and in the few patients analysed in detail at 1200mgm. and 1400mgm. of sodium valproate daily ($P = 0.025$ respectively). This means that with increased dosage, as the PCR sensitivity range recedes, the on-going process towards significant improvement or total abolition of photosensitivity involves the breakdown of the PCR into residual abnormality.

7.11.3. Onset of the PCR.

The onset, persistency and maximal amplitude of the PCR, regardless of form, were measured prior to treatment and at each dosage of sodium valproate. Where several EEGs were recorded at a particular dosage, then the EEG showing the most favourable improvement in the sensitivity range was used for analysis.

Onset measurements for each PCR were obtained by dividing the 2-second flash stimulus into four half-second sections and labelling them 1 - 4. It is known that PCRs may occur within the first second of a train of flashes or in the middle of a flash period (Jeavons and Harding 1975). The second immediately following termination of IPS was labelled as 5 and 6 but PCR initiations here were generally considered

as off- responses. On the basis of Jeavons and Harding (1975) study, single slow waves, spikes, or non-persistent spike and wave confined to the initiation of the flash stimulus (on-responses) were ignored.

Due to the ordinal nature of the results, Wilcoxon's Matched Pairs Signed Ranks non-parametric test was employed. Because of the nature of this statistic, too many ties occurred between pre-drug findings and both 1000 mgm. and 1200 mgm. to determine whether any significant differences existed in the minimum and maximum values for range of PCR onset, and similarly at 800 mgm for maximum time of onset. However, comparison between pre-drug levels and 800 mgm. was possible for minimum time of onset which showed that at this dose of sodium valproate the PCR occurred significantly later within the 2-second flash stimulus, than before treatment ($P = 0.025$, 1 tailed test).

7.11.4. Persistency of the PCR.

Series of parametric correlated t tests were conducted between the maximum pre-drug PCR duration and that at 800, 1000 and 1200 mgm. of sodium valproate. At 800 mgm. one patient was also taking phenytoin which was further reduced at 1000 mgm.. At this dosage another patient also received phenobarbitone. No patients were taking additional anticonvulsants at 1200 mgm. For those patients with or without other medication , the duration of the PCR was significantly lower at all dose levels of sodium valproate ($P \leq 0.05$, 1 tailed tests) in comparison to pre-treatment measures (Table 7.6.). Similar results were obtained even when the cured patients, i.e. zero duration, were excluded from analysis.

Dosage	PCR Duration (sec)		PCR Amplitude (MV)	
	Mean	S.D	Mean	S.D.
Pre-drug (P_2)	3 · 09	2 · 43	339 · 38	31 · 47
800 mgm.	2 · 14	0 · 75	277 · 92	62 · 70
1000 mgm.	1 · 86	0 · 37	300 · 0	43 · 43
1200 mgm.	1 · 58	0 · 31	270 · 0	53 · 54
Last - Treatment	1 · 45	0 · 33	271 · 43	54 · 62
Post - drug	2 · 44	0 · 39	328 · 46	33 · 01

Table 7.6. Structural changes of the PCR during Sodium Valproate treatment.

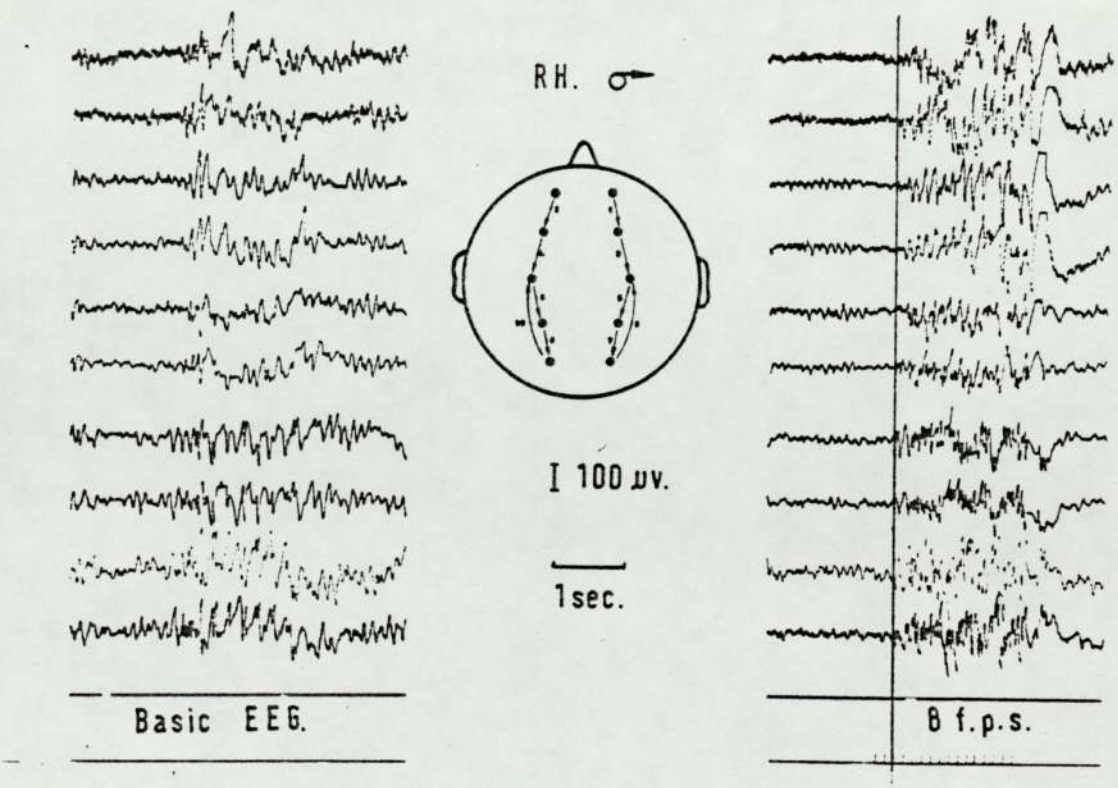


Fig. 7.9. Spontaneous EEG abnormality of irregular, mainly theta spike and wave, differs from the Polyspike PCR evoked by IPS at 8 f.p.s with simultaneous spread to all regions.

From the detailed EEG analysis of 13 withdrawal patients, the duration of the PCR obtained at the last-treatment EEG prior to cessation of therapy was still significantly lower than pre-drug PCR duration ($P = 0.025$). However, within an average period of 2.77 months after withdrawal, the duration of the PCR did not differ significantly from that seen before treatment; on average 1 year 7 months (S.D. 8.4 months) previously ($t = 0$, df12, $P > 0.05$).

It can be concluded that even at low dosage, sodium valproate was effectively reducing the duration of the PCR, but after a short period of drug withdrawal, pre-drug persistency returned.

7.11.5. Amplitude of the PCR.

The maximal amplitude of the PCR, as recorded from the occipital to rolandic derivations ($O_1 - C_3$ and $O_2 - O_4$) was compared between the last EEG prior to treatment and each dosage of sodium valproate for those patients still possessing a PCR. At 800 mgm., 1000 mgm. and 1200 mgm. the amplitude of the PCR had significantly reduced from pre-drug levels for all patients with or without additional medication (Correlated t tests, $P \leq 0.05$, 1 tailed). The last treatment EEG investigation just prior to commencement of withdrawal of sodium valproate still showed that in the few patients exhibiting a PCR, the amplitude was still significantly reduced in comparison to pre-drug levels ($t = 2.95$, df 6, $P = 0.025$). However, after withdrawal the PCR increased in amplitude to the level seen before treatment ($t = 1.20$, df 12, $P > 0.05$).

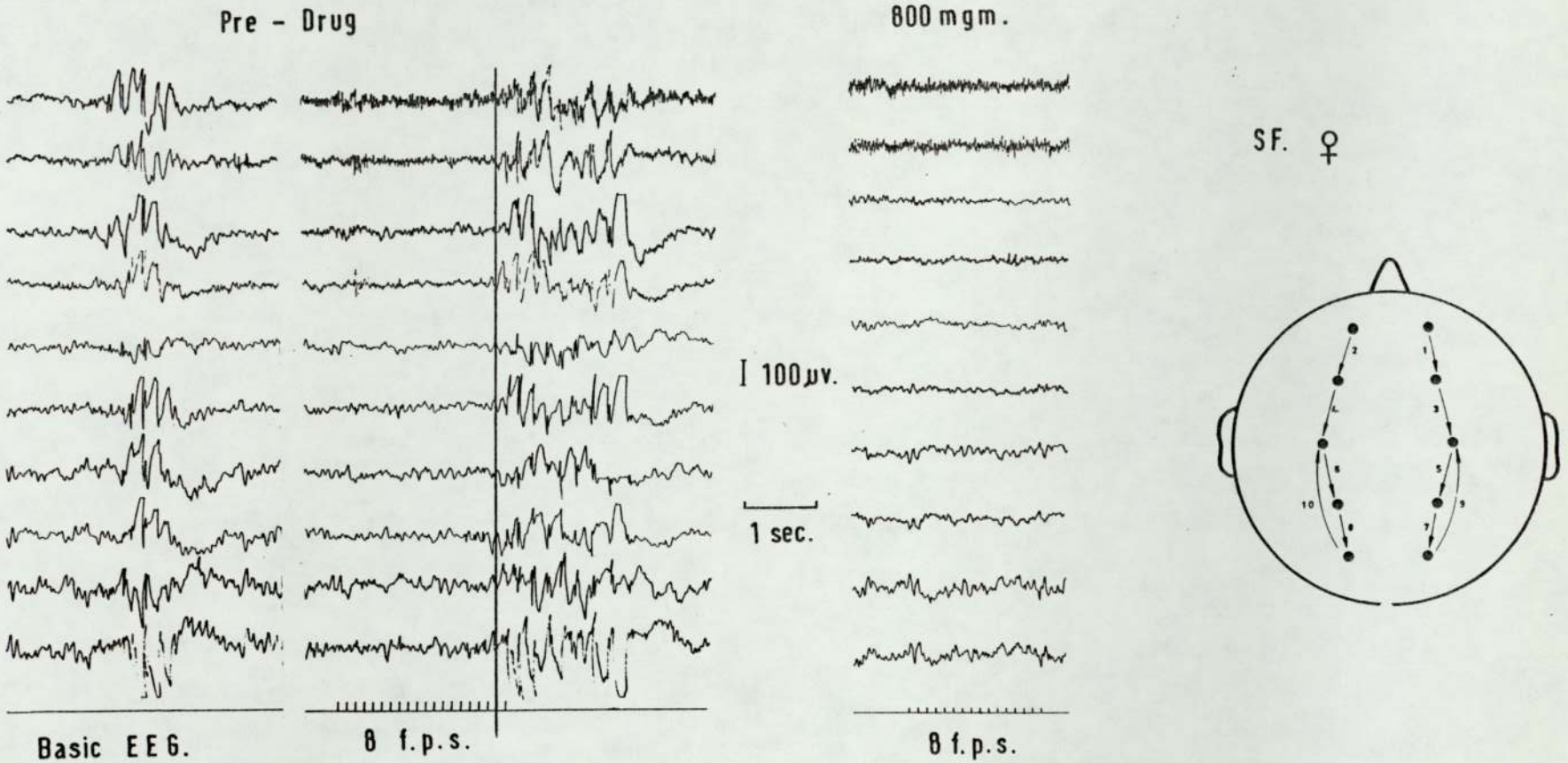


Fig. 7.10. Atypical Spike and Wave PCR (with Occipital Spike precipitation at 8 f.p.s.) and similar spontaneous EEG abnormality (but occurring simultaneously over all regions) disappear at an optimum dosage of 800 mg/day Sodium Valproate.

The above findings show that the nature, onset, persistency and amplitude of the PCR are of definite value when monitoring therapy in the photosensitive patient. Even at low dosage, sodium valproate begins to detensify the PCR. As dosage increases towards the optimum level, producing a significant reduction in the incidence of the true PCR, the process is reflected in the degradation of photically evoked abnormality. The onset of the spike and wave discharge becomes delayed, it is less persistent and of lower amplitude. These effects begin to occur before optimum dosage is reached and are proved to be due to the direct action of sodium valproate, as drug withdrawal causes a return to the pre-treatment nature and persistency of the PCR.

7.12. Occipital Spikes.

Occipital spikes are often a characteristic feature in the photosensitive EEG. Dimitrakoudi et al. (1973) reported that of 46 patients 67% had occipital spikes visible in the EEG which increased to 91% with VEP analysis. Therefore, unless the investigator is specifically looking for occipital spikes, they may be overlooked. From the 254 untreated population of photosensitive patients (see Section 5.2.2.), the EEG reports quoted 130 (51.2%) as having occipital spikes. No significant difference existed between the number of patients with spikes and those where occipital spikes were non-apparent. (χ^2 = 0.2, df1, P > 0.05); neither was the presence or absence of occipital spikes dependent on being male or female (χ^2 = 0.71, df1, P > 0.05), nor was it influenced by the patient's clinical history (χ^2 = 1.17, df2, P > 0.05). All three photosensitive groups had an approximately 50% occurrence of occipital spikes and despite the variation in seizure types between groups (see Section 5.2.2.), no significant trend was observed in relation to seizure type and the presence or absence of occipital spikes.

The distribution of occipital spikes, either occurring at low flash rates with the photic driving response or as a PCR precipitator at the lower limit or upper limit, was determined for the 29 patients attending the Neuropsychology Unit, intended for sodium valproate treatment. Before therapy, occipital spikes were observed in the EEGs of 19 patients. The other 10 patients showed no evidence of occipital spiking during IPS. This difference proved to be significant at the 5% probability level (χ^2 = 2.80, df1). Fig. 7.11. and Table 7.7. show the occurrence of occipital spikes at the various dosages of

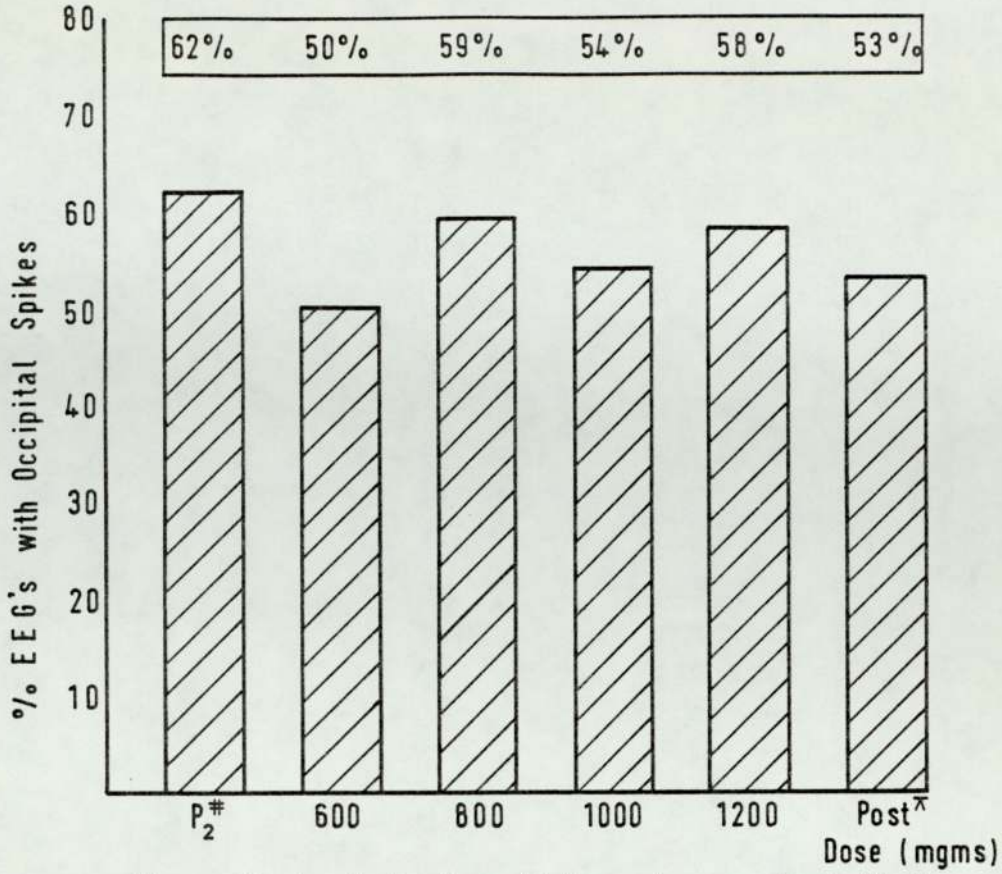


Fig. 7.11. The effect of Sodium Valproate on Occipital Spikes in the EEG during Photic Stimulation

Dose	No Occipital Spikes	Occipital Spikes	Total
$P_2^{\#}$	11 (38%)	18 (62%)	29
600	2 (50%)	2 (50%)	4
800	7 (41%)	10 (59%)	17
1000	11 (46%)	13 (54%)	24
1200	5 (42%)	7 (58%)	12
1400	0	3 (100%)	3
Post^	7 (47%)	8 (53%)	15

Table 7.7. Distribution of Occipital Spikes during Phetic Stimulation at dose levels of Sodium Valproate # (P_2 = 2nd Pre-Epilim record; ^ Post = Post-Epilim record)

sodium valproate. It is evident that even 1200 mg/day had no no effect on this abnormality.

Of the 19 patients with occipital spikes in their pre-drug EEGs 9 lost these spikes and 10 retained the spikes during sodium valproate treatment (χ^2 = 0.06, df1, P > 0.05). In the 9 'spike-free' patients one, having achieved a 71% improvement in photosensitivity, was left with ill-defined mid-responses in the upper half of his original sensitivity range. Previously his occipital spikes had been present at 5-7 f.p.s. and precipitated PCRs at the lower limit of 7 f.p.s.. The other 8 patients all reached total abolition of photosensitivity. Of these, 4 patients previously had single occipital spike precipitation of the lower limit. Four others were considered as having had persistent occipital spikes which were combined with the driving response in all cases, but also precipitated the lower limit in 2 patients and both the lower limit and upper limit in the other 2 cases.

From the 19 patients with pre-drug occipital spiking, 12 reached total abolition of photosensitivity and 7 either showed marked or no improvement. Significantly more patients attaining a cure lost their occipital spikes than those patients still showing residual or marked photosensitivity (Fisher-Yates contingency test, P = 0.04).

Of the 10 patients who kept their occipital spikes during treatment, 4 reached total abolition, 3 significant improvement of photosensitivity and 3 others did not improve markedly. All patients had persistent occipital spikes at low flash rates with lower limit precipitation in 6 patients and PCR precipitation at both the upper and lower limit in

another 4 patients. Significantly more patients with persistent occipital spiking in the pre-drug EEG kept their occipital spikes during sodium valproate treatment than those patients with single occipital spike precipitation of the PCR (Fisher-Yates Contingency test, $P = 0.033$).

A comparison between patients reaching a significant improvement in photosensitivity ($\geq 78\%$) and unimproved patients ($< 78\%$) at optimum dosage showed no significant difference in occipital spike frequency (Fisher-Yates) Contingency test, $P = 0.07$).

No significant differences were found between 3 photosensitive clinical groups as regards the distribution of occipital spikes at the pre-drug EEG and at optimum dosage (Fisher-Yates Contingency test $P > 0.05$). However as regards the patients who were clinically sensitive to television, regardless of whether spontaneous fits also occurred, significantly more were found to have occipital spikes prior to treatment than patients whose fits were not triggered by television ($\chi^2 = 3.52$ df1, $P = 0.05$). No clinical group differences were observed between the patients who lost or retained their occipital spikes at optimum dosage (Fisher-Yates Contingency test, $P > 0.05$), and similarly no significant difference was observed between television sensitive and other clinically photosensitive patients (Fisher Exact Probability test, $P = 0.09$).

No significant difference was found between males and females for the presence or absence of occipital spikes prior to treatment, nor in those patients who lost or retained occipital spikes at optimum dosage (Fisher-Yates Contingency test, $P > 0.05$ respectively).

Of the 16 patients who withdrew from sodium valproate, occipital spike data was available on 15 patients. Spikes were present in 9 patients and absent in 6 at the pre-drug EEG. No significant difference was found between the presence or absence of spikes prior to treatment, at optimum dosage and after withdrawal of sodium valproate (Binomial tests, $P > 0.05$); neither were there any significant changes from a presence to absence or vice versa of occipital spikes between the pre-drug EEG and optimum dosage, optimum dosage and the post drug EEG or before treatment and after withdrawal of sodium valproate, (McNemar tests, $\chi^2 \leq 0.25$ df1, $P > 0.05$).

In conclusion, the presence of occipital spikes in the EEG during IPS is not related to sex-type or clinical group as regards flicker-sensitive or spontaneous fits. However, occipital spikes tend to be more common in patients who have all or some fits precipitated by television. Treatment with sodium valproate shows no differential effect between clinical groups or males and females. Occipital spikes are slow to respond to therapy and are likely to be present even after a significant reduction has occurred in overall photosensitivity. However, when occipital spikes are related to the PCR as brief precipitators, they usually disappear when sodium valproate treatment results in total abolition of the PCR.

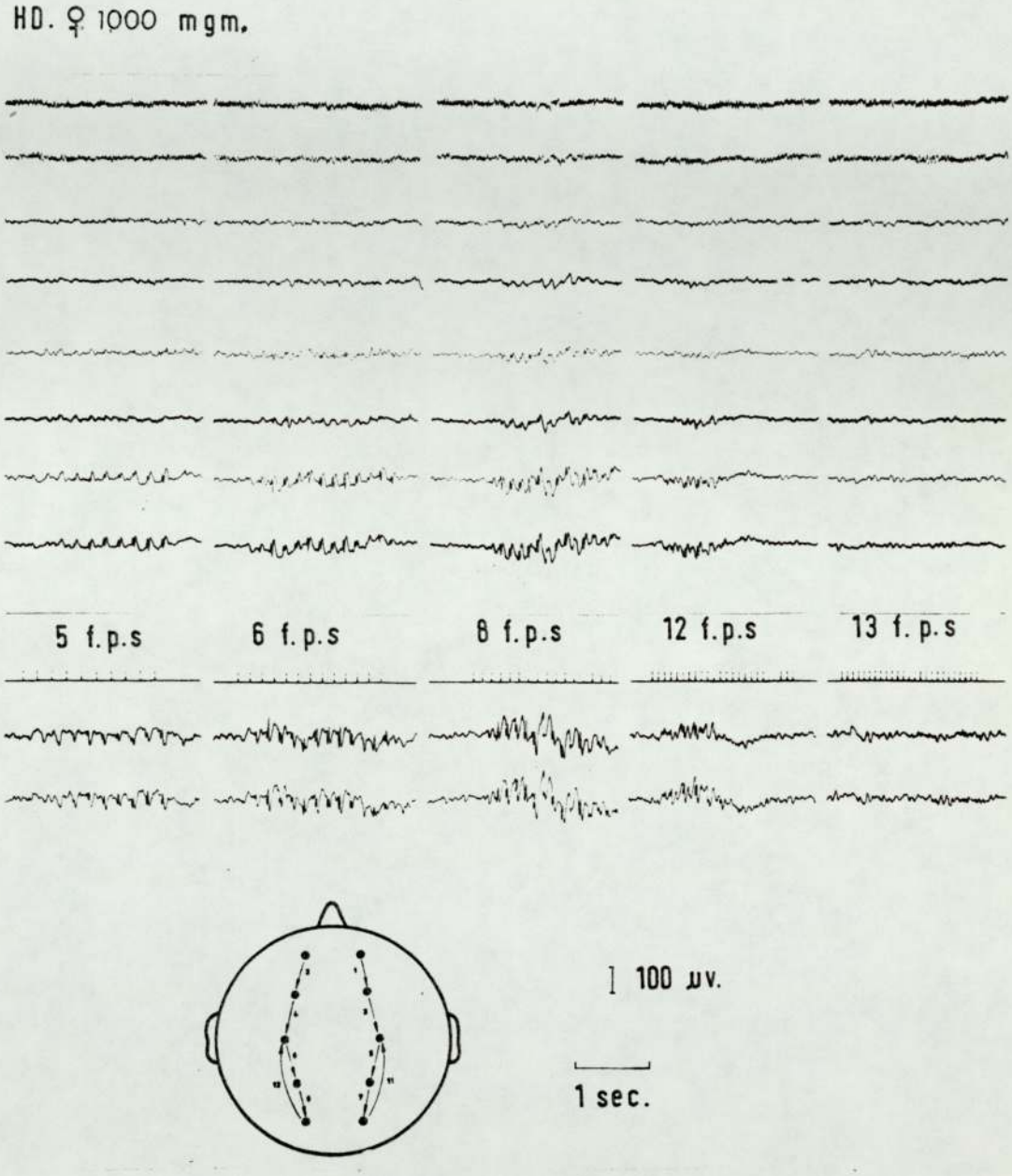


Fig. 7.12. Photic Driving with Occipital Spikes from 5 – 12 f.p.s. in a patient with no PCRs at Optimum dosage of Sodium Valproate.

7.13. Photic Driving.

The rhythmical physiological following response to light stimulation (photic driving) was visually analysed over the posterior EEG derivations. Although fundamental, harmonic and sub-harmonic responses were classified it was noted in photosensitive patients and normal, healthy control subjects that the presence of higher order harmonics was variable and it was frequently possible to detect a mixture of fundamental and harmonic responses at any particular flash frequency. The range of frequencies and the frequency limits for the presence of photic driving were therefore determined in the 29 photosensitive patients attending the Neuropsychology Unit. The criterion for a positive result was the occurrence of at least one second of photic driving within the two second IPS stimulus. All parameters were compared to age and sex matched normal control subjects. When 'islands' of photic driving occurred between the lowest and highest frequency producing a response, the actual number of frequencies for photic driving was determined in a similar manner as for the photosensitivity range (see Section 7.1.1.).

Prior to treatment, no significant difference was found for the upper frequency limit and the photic driving range between photosensitive patients and controls ($P > 0.05$). However, in the photosensitives, photic driving was observed at significantly lower flash frequencies ($t = -4.35$ df22, $P = 0.0005$). At optimum dosage of sodium valproate and after withdrawal of the drug exactly the same effects existed. The upper limit and overall frequency range was not significantly different between patients and controls but photic driving still occurred at lower flash rates in the photo-

sensitive patients, even after significant improvement in photosensitivity ($t = -1.81$, df18, $P = 0.05$) and within 7 months of sodium valproate withdrawal ($t = -3.38$ df9, $P = 0.005$).

7.14. Side Effects.

Side effects of treatment ranged from insignificant (transient indigestion or change in appetite) to severe (nausea/sickness) upsets. Of all the 50 patients, 17% reported transient feelings of nausea, heartburn or discomfort in swallowing the tablets. These effects usually disappeared when the patients followed instructions to take their tablets after a meal, or with a long drink of milk or water. However, 5 patients (10%) suffered definite gastric upset of vomiting or severe abdominal pain, at times associated with giddiness. In 4 patients these symptoms were the result of an increase in drug dosage to 1200 or 1400 mg/day. Two patients were withdrawn from therapy, one patient stopped attending and, in two others, the dosage was recorrected.

Four patients (8% - 2 males and 2 females) developed curly hair. One male patient had hair loss, prior to curliness. All patients except one were taking sodium valproate alone. The other patient was also receiving ethosuximide and phenytoin.

Increased appetite with associated gain in weight was reported by 7 patients, which included 5 females and 2 males. However, this may have been an idiosyncratic effect. These patients were aged between 13 and 20 years and overall 27 of the 50 patients were aged less than 15 years, when growth was still rapidly occurring. Weights were obtained for patients before, during and after sodium valproate treatment. The changes in weight between the last pre-drug EEG, optimum dosage, last-treatment and post drug EEG for individual patients were compared to standard weight alter-

ations, obtained from Growth and Development Charts (Tanner and Whitehouse 1959), that should have occurred for the particular age increase between any two of the EEGs. No significant differences were found between the actual loss or gain in weight and estimated standard weight gain for patients at optimum dosage in relation to their pre-treatment weights ($t = -0.19$ df14, $P > 0.05$), or after withdrawal of sodium valproate in relation to weight measured at the last treatment EEG ($t = -1.73$ df11, $P > 0.05$). Similarly, sodium valproate exerted no after-effects on weight as shown by the lack of significance between actual weight change and estimated weight change between the pre- and post-drug EEGs ($t = 0.42$ df4, $P > 0.05$). Therefore after a period of treatment ranging from 1 month to 2 years 4 months, sodium valproate overall did not cause unusual gains in weight and neither did a mean period of 2.86 months (S.D. 1.73 months) drug withdrawal produce significant weight changes.

Three patients had complicating migraine during therapy. A family history of migraine existed in two siblings and the younger, male sibling (10 years 8 months) had also suffered attacks before sodium valproate therapy. However, 5 months after treatment and an increase from 400 to 1000 mg/day, his attacks worsened. At the same time, his sister (13 years 9 months), also having undergone this increase in dosage, started with migrainous headaches. In both patients migraine was associated with photophobia. Migraine began in another male patient (18 years 4 months) after receiving sodium valproate for 1 year 7 months during which time he was taking 1200 mg/day for 1 year 4 months. The involvement of drug effects was therefore doubtful and his headaches had been

associated with emotional upset and eating plain chocolate when watching television.

One female patient, on a 1000 mg/day of sodium valproate alone, miscarried after 2 months of pregnancy. There was no conclusive evidence that this had been due to drug treatment. Before therapy she had been poorly controlled on other drugs and suffered with absences, tonic-clonic and myoclonic seizures. She remained on sodium valproate which abolished her photosensitivity and fully controlled her epileptic attacks. Another female patient with a clinical history of photosensitive fits and spontaneous seizures, particularly associated with her menstrual phase, had been on 1000 mgm. of sodium valproate daily for 8 months and the contraceptive pill (Gynovolar) for 5 years. She discovered that by only taking sodium valproate for the first three weeks of her menstrual cycle could she menstruate regularly. Janz and Schmidt (1974) reported three cases of idiosyncratic interactions between contraceptive pills and other anticonvulsants in which pregnancy occurred due to failure of the contraception. However, in the present study, 3 other female patients took sodium valproate and contraceptive pills (Eugynon, Microgynon or Minovular) without any contraindications. In these patients clinical fits had not been directly linked to the menstrual cycle.

Of the 50 patients, it was determined that 8 (16%) showed definite evidence of side-effects as a result of sodium valproate treatment.

7.15. Clinical Effects.

Table 6.3. illustrates the distribution of seizures amongst the 50 photosensitive patients. The majority, 86%, had a clinical history of tonic-clonic fits but 36% of patients had two or more types of seizures either in association with tonic-clonic or other varieties of attacks. One patient was referred solely with a history of syncope and feeling 'funny' when watching television.

Only 10 patients had purely spontaneous fits (Group III), whereas 16 patients also had seizures precipitated by flicker besides spontaneous attacks (Group II), and 22 had fits only as a result of precipitation by flickering light stimuli (Group I). All the 38 clinically flicker-sensitive patients had had one or more fits triggered by television. Therefore, as the majority of patients previously suffered attacks due to the direct action of a critical stimulus, it was not possible to assess any clinical criteria for seizure improvement. Even before therapy, patients were instructed to adopt avoidance procedures when faced with flickering light. However, 10 of the 38 television sensitive patients were compulsive viewers, i.e. they were inexplicably drawn towards the screen. Before therapy, this reaction had been restrained in one patient by changing to a colour television. In the other 9 patients, the impulsive attraction stopped during sodium valproate treatment, even in one patient who only showed a 15% improvement in his photosensitivity. Another patient noted that after withdrawal of the drug she again felt drawn towards the television screen.

Of the 48 epileptic patients, 6 continued to have

attacks at some point during therapy. However, 2 patients were suspected of being incompliant in taking their required dosage. One 16 year old girl missed all her tablets for three days and subsequently had a tonic-clonic fit while walking past some railings on a sunny day. The other patient, a 15 year old male, having been prescribed 1200 mg/day of sodium valproate in conjunction with reduced dosages of phenobarbitone and ethosuximide, had a return of eyelid myoclonia. The attacks ceased when the other drugs were terminated, possibly due to him becoming more conscientious in taking the reduced number of tablets and, therefore, full dosage of sodium valproate. As regards the 4 other clinically relapsed patients, one female (Group II) had an attack due to fluorescent lighting reflected off a radiator but had only attained 35% photosensitive improvement. Another patient (Group II), although achieving a 93% improvement while receiving 1200 mgm. of sodium valproate and phenytoin, had a return of her tonic-clonic fits, myoclonic jerks and eyelid myoclonia. Absence seizures were gradually reduced in a male adult patient (Group III) taking 1200 mg/day of sodium valproate. Similarly a female patient (Group II) became free from mixed seizures as dosage was increased from 800 mgm. to 1000 mg/day. One other patient (male aged 24 years), although clinically free from attacks Group III) at 1000 mg/day, had a tonic-clonic fit during IPS in the laboratory; dosage was increased to 1200 mgm, resulting in total abolition of photosensitivity and seizures.

Within 1-7 months after withdrawal of sodium valproate,

4 of the 16 patients had seizures. In 2 patients (Group I) television and flickering 'fairy lights' precipitated tonic-clonic attacks; spontaneous myoclonic jerking and eyelid myoclonia returned in another patient (Group II); the fourth patient (Group II) had a spontaneous tonic-clonic fit.

Overall, 31 patients before sodium valproate treatment had a clinical history of generalised seizures; 3 had minor seizures and 14 had mixed seizures of generalised plus minor or focal attacks. No significant differences were found between these epileptic groups for the dgree of improvement in photosensitivity ($P > 0.05$).

7.16. Subjective Sensations.

Thirty-nine patients received sodium valproate alone and 11 patients retained reduced dosages of other anti-convulsants None reported depression or any adverse psychological disturbances during treatment. In fact many patients experienced a sense of well-being. As patients were always informed of their progress, this may have been partly due to increased self-confidence as EEG improvements increased. A few children, previously restricted by their parents because of their epilepsy, were now allowed to ride bikes and go swimming, much to their pleasure. Surprisingly, in one youth his severe acne cleared quite quickly while receiving sodium valproate.

Most patients previously bothered by television or other environmental flickering light reported that they were now unaffected, although a few still adopted the usual precautions. However, one patient still found that intense flashing lights in discotheques caused 'peculiar sensations', even though her EEG showed total abolition of photosensitivity. Tiredness and memory lapses occurred in one female patient receiving a 1000 mg/day of sodium valproate as well as phenobarbitone and ethosuximide. This was probably the result of increased phenobarbitone serum levels (see Section 4.8.).

8. PATTERN: INFLUENCE ON PHOTOSENSITIVITY AND THE VISUAL EVOKED POTENTIAL

8.1. Rationale for the Study.

There have been many anecdotal reports but few scientific studies into the effects of pattern on photosensitivity since a very early observation that sunlight streaming through a wire meshed window aggravated myoclonic jerking in a female photosensitive patient (Goodkind 1936). The condition where simple pattern presentation evokes spike and wave paroxysms is rare (Bickford and Klass 1969). However, these individuals are generally also sensitive to photic stimulation (Chatrain et al. 1970a; Wilkins et al. 1975). Similarly, patterns combined with IPS greatly increases the probability of a PCR in patients with photosensitive epilepsy (Jeavons et al. 1972b). In fact the mechanism whereby pattern enhances the efficiency of IPS in these patients has been linked with that in pattern-sensitive epilepsy (Jeavons and Harding 1975). They suggest that the difference between the two conditions is that flickering light is more potent in photosensitive epilepsy than patterns alone, whereas patterns are more provocative than flicker in pattern-sensitive epilepsy.

Investigations into the triggering effect of pattern itself or in combination with IPS have shown that highly contrasted, fine geometric patterns with elements of 11' - 24' visual angle are most effective (see Section 2.5.). These results are in close agreement with the findings for VEP recording with flashed-pattern or pattern-reversal stimulation. Breaks in contours and the presence of corners appear to be

the most crucial factors in producing maximum VEP amplitudes (White 1974). There is general agreement among authors that the optimum square size for eliciting evoked potentials is within 10' - 30' visual angle (Spekreijse 1966; van der Tweel and Spekreijse 1966; Eason et al. 1970; Harter and White 1970; Cigánek 1971; May et al. 1971; Lesèvere and Rémond 1972).

The amplitude of the pattern VEP is also dependent upon the area of retinal stimulation. Several studies have indicated that the pattern response is mostly generated by the central fovea (Spekreijse 1966; Rietveld et al. 1967; May et al 1971; White 1974). Pattern stimulation of the macular also had marked epileptogenic effects in pattern-sensitive epilepsy in contrast to the effectiveness of peripheral retinal stimulation (Chatrian et al. 1970a). Physiological evidence supports these findings. ERG studies revealed that the spectral luminosity curve of pattern stimulation is photopic, whereas for diffuse light it is both photopic and scotopic, indicating that mainly cones, of maximal density in the rod-free fovea, are involved in the primary reception of pattern perception (Johnson, Riggs and Shick 1966). In the primary visual cortex, there is greater representation of the macular than the peripheral retina which is also placed closer to the vicinity of the scalp than regions receiving projections from other retinal areas (Regan 1972). In primates, micro-electrode experiments revealed that the neurons of the primary visual cortex respond to contrast and contour of specific dimensions and not to diffuse light which stimulated both excitatory and inhibitory regions of receptive cells and greatly reduced or abolished firing of cortical cells (Hubel and Wiesel 1959, 1962; 1968).

Comparing the efficacy of plain flash, diffused flash and patterned flash of large and small square grids, horizontal and vertical lines, Jeavons et al. (1972b) found that the grid pattern subtending small squares at a 22' visual angle was the most effective flash stimulus for evoking PCRs and recommended its routine clinical use. However, contrary to these results, Engel (1974) reported that patterned flash was not necessarily better than diffuse flash for evoking PCRs. Using a Devices Type 3180 photostimulator with a translucent screen, he presented either the plain flash or superimposed a black and white checkerboard pattern with squares at 20' subtense. In over 100 patients with definite or suspected epilepsy or other neurological disorders, 28 cases exhibited consistent PCRs. Sixteen patients were sensitive to both diffuse and patterned flash, 7 only to the diffuse flash and 5 showed sensitivity only to the patterned flash. Jeavons and Harding (1975) replied that the discrepancy between Engel's and their findings was that the use of a checkerboard pattern would effectively block out half the lamp and greatly reduce the stimulus intensity. They believed that their own fine grid pattern had less effect on intensity than the checkerboard pattern.

8.2. The Photosensitivity Range.

8.2.1. Laboratory technique and pattern stimulation.

An experiment was devised to test the relative effects of plain diffused photic stimulation and patterned flash on the photoconvulsive propensity. Routine EEG recording was made as described in Section 7.1. using a para-saggital montage. Ten photosensitive patients were examined, ranging in age from 10 years 2 months to 23 years 1 month (mean 15 years 4 months, S.D. 3 years 7 months). Nine patients had a clinical history of epilepsy. Five patients were in Group I (photosensitive fits only), 3 were in Group II (spontaneous and photosensitive fits) and 1 patient was in Group III (spontaneous fits only). Onset of fits and preliminary EEG referral had originated between the ages of 4 - 15 years. The remaining patient was fit-free, but had been referred with a history of 'blackouts '. She also reported feeling 'queer' when approaching too close to the television. Onset of syncopal attacks and first evidence of laboratory photosensitivity was at 18 years of age.

All patients were routinely tested for photosensitivity with eyes-open and closed using a Grass PS22 stroboscope at 1,363 nits (intensity setting 2) on which was affixed a grid pattern of squares at a 26' visual angle. No patient was receiving sodium valproate treatment. However, one patient received a single, nightly dose of tryotosal, another was taking phenytoin and phenobarbitone and the non-epileptic patient received sodium amytal.

The effectiveness of four further photic stimuli was then compared in a random order :-

(i) Diffused flash at intensity 2 (1,363 nits);

(ii) A grid patterned flash with thin black lines, at intensity 2. Each small square subtended a 12' visual angle;

(iii) A small squared (12') black and white checkerboard patterned flash at intensity 2;

(iv) The checkerboard pattern (12' square subtense) at intensity 4 (1,925 nits).

The grid pattern was a self-adhesive transparency Artype No. HR 4149 and the checkerboard was made by blacking-in every other square with indelible ink. Pattern elements of 12' subtense were selected for optimal stimulation of the fovea. In order to present these dimensions, the lamp was placed at 42.5 cm away from the patient's open eyes. At this distance the overall visual angle of stimulation was $17^{o}23'$ which, according to the neural representation formula of Drasdo (1977) stimulates 63% of the visual information capacity. Each pattern was superimposed in front of the diffused flash. Light transmission was effectively reduced to 40% of the plain flash by the grid pattern and to 32% by the black and white checkerboard. This meant that the resulting illuminance of the checkerboard at intensity 4 (1,925 nits) was 13% greater than that of the grid pattern, with the same dimensions, at intensity 2 (1,363 nits). However, retinal illuminance by the diffused flash at intensity 2 was double (221%) that of the checkerboard pattern at intensity 4. For each stimulus the sensitivity range and its lower and upper limits were determined as described in Section 7.1.1..

8.2.2. Effect of diffuse and patterned IPS on the sensitivity range and occipital spikes.

A significant variation was found between patients in the sensitivity range and lower limits for all four stimuli (Analysis of Variance, $P = 0.01$). However, there was no significant variation among patients as regards the upper limit of sensitivity for each pattern ($P > 0.05$).

The mean sensitivity ranges were 18.8 f.p.s. for the diffused flash, 26.8 f.p.s. for the checkerboard pattern at intensity 2, 27.3 f.p.s. for the checkerboard at intensity 4, and 29.1 f.p.s. for the fine grid patterned flash. The sensitivity range obtained during stimulation with the diffuse flash was significantly lower than that for the grid pattern flash ($t = -1.93$ df9, $P = 0.05$). Both checkerboard patterned stimuli appeared to have intermediary effects. No significant differences were observed between these two patterns or between either stimulus and the plain or grid flash stimulus ($P > 0.05$).

Similarly, the lower limit of the sensitivity range during diffuse IPS occurred at a significantly higher flash rate than that of the grid patterned flash ($t = 2.43$ df8, $P = 0.025$). No significant differences were found from comparisons between all other stimuli ($P > 0.05$). The mean flash frequencies for the lower limit were at 17.11 f.p.s. for the diffuse flash, 13.11 f.p.s. checkerboard flash at intensity 2, 12.78 f.p.s. checkerboard flash at intensity 4 and 12 f.p.s. for the grid stimulus.

No significant differences were observed between any of the 4 flash stimuli as regards the upper limit of the sensitivity range ($P > 0.05$). Photic stimulation with the

diffuse flash gave a mean upper limit of 40.44 f.p.s., a mean of 39.89 f.p.s. for the grid pattern, 39.44 f.p.s. with the checkerboard at intensity 2, and 39.22 f.p.s. with the checkerboard at intensity 4.

At the lower limit, the probability of occipital spike precipitation of the PCR was significantly different under the 4 stimulus conditions (Cochran Q test, Q = 11.8 df 3, P = 0.01). Only 2 out of the 10 patients exhibited occipital spikes at the lower limit of photosensitivity with diffuse IPS and, in 1 of these 2 patients, the spikes occurred inconsistently. Six patients had PCRs triggered by occipital spikes during IPS with the checkerboard pattern at both intensities. The flashed grid pattern elicited occipital spikes in 7, one of whom had spikes only with this type of patterned IPS, taking the form of a single occipital spike which triggered the PCR. This patient was the syncopal case who exhibited her widest sensitivity range during IPS with the diffuse stimulus. Overall occipital spikes were very infrequent in response to the diffuse flash and, of the patterned stimuli, they occurred more consistently with the grid pattern.

At the upper limit, there was no significant difference between the patterned and diffuse flash for the incidence of PCR precipitation by occipital spikes (Cochran Q test, Q = 5.18 df3, P > 0.05). Occipital spikes occurred in 2 patients during diffuse IPS and in 3 patients with the checkerboard patterns at both intensities. However, the spikes always occurred inconsistently with the unpatterned stimulus and the checkerboard pattern at the lower intensity. Five patients had triggering of upper limit PCRs under the grid pattern, although again in 4 patients occipital spikes were inconsistent.

It follows, therefore, that when two-thirds of the visual information channels were potentially stimulated, maximal foveal stimulation with a fine grid pattern of 12' square subtense was significantly more effective than a diffuse flashing light in evoking PCRs . However, checkerboard patterned flash of the same dimensions appeared to exert an intermediary effect and, although variation in photosensitivity between this pattern (both at a high and low intensity) and the diffuse or grid patterned flash were non-significant, the overall sensitivity ranges and lower limits were more similar to the grid pattern than to the unpatterned flash. Intensity does not appear to be an important factor in the comparison between the patterned and unstructured stimulus field as the retinal illumination from the diffused light was far greater than from any of the patterned stimuli. Also it was the grid pattern, with a lower transmission intensity than even the checkerboard pattern at intensity 4, that was the most provocative stimulus.

The most crucial factor contributing to the differentiation between stimuli was the lower limit of photosensitivity. This occurred at a significantly lower flash frequency with the grid pattern than with the diffuse IPS. The upper limit showed less discrimination between each type of flash stimulus. Also, the precipitation of spike and wave by occipital spikes varied significantly at the lower flash frequencies and it was notable that spike occurrence was most infrequent during diffuse photic stimulation and most consistent under the grid patterned flash. At fast flash rates, however, any occipital spikes were generally inconstant and no differentiation was observed between the stimuli.

It seems, therefore, that the effect of pattern on the photo-convulsive propensity operates at the lower end of the frequency range where its influence over-rides that of light intensity, whereas at the higher frequencies it is the flickering light per se which mainly appears to determine the photosensitive response.

It is therefore probable that if Engel (1974) had compensated for the intensity factor between his checker-board pattern and diffuse flash, his results would not have been significantly altered. However, testing with a grid pattern may have increased the photosensitive response of those patients, in his series, sensitive to the checkerboard patterned IPS. In the present study, large individual differences were found between patients in their lower limit and consequently sensitivity range, within each stimulus. At one extreme, a female patient (Group I) had a sensitivity range of 31 f.p.s. with a lower limit at 6 f.p.s. during IPS with the grid pattern. She was, however, totally insens-itive to the diffuse flash. At the other extreme both the checkerboard patterns elicited a PCR at only a single flash rate (45 f.p.s.) in the non-epileptic patient with a clinical history of syncope. Photic stimulation with diffuse IPS evoked her widest sensitivity range (22 f.p.s.) with a lower limit at 27 f.p.s..

Engel (1974) found that all 7 patients who were photosensitive to diffuse light also suffered different dis-orders from the remaining patients who were, either or also, sensitive to patterned flash. Two patients had neuro-logical trauma (e.g. stroke) preceding their photosensitivity. The other 5 had histories of 'black-outs' unaccompanied by

motor activity, no myoclonic jerks or absence attacks and only one of these patients suffered generalised motor seizures. It was also significant that, of the entire group, all patients with adult onset of epilepsy, after 18 years of age, were sensitive only to the plain flash. It is interesting that the one non-epileptic patient in Engel's series was more sensitive to the plain than patterned flash as was the syncopal patient in the present study. Also, as previously mentioned, this patient began her 'attacks' at 18 years, whereas the photosensitive epileptics, particularly sensitive to flashed-pattern, had clinical onset during childhood, between the ages of 4 - 15 years.

Photosensitivity is believed to be the expression of a gene-controlled hyperexcitability with maximum penetrance between 5 - 15 years of age (Gerken et al. 1968; Doose et al. 1969a, b). Onset of the PCR was found by Jeavons and Harding (1975) to be strongly linked with puberty as modal onset in a large photosensitive population was at 12 years, and the mean at 13.7 years. It is possible that in patients sensitive only to plain or diffuse IPS, with adult onset of epilepsy or neurological disorder, the underlying mechanisms may not be the expression of a constitutional functional instability. Also, as mentioned in Section 8.1. diffuse light and pattern information are thought to be mediated by different pathways. However, whereas the former pathway appears to be operating alone in patients purely sensitive to diffuse light, the similarity between the upper limits and diversity of the lower limits between patterned and diffuse flash sensitivty indicate that both mechanisms may be operating in photosensitive epilepsy. Indeed Engel (1974)

found that a pattern-reversal stimulus without alteration in the overall level of illumination was completely inadequate in eliciting PCRs. Unpublished findings by the present author support this observation. It therefore appears that in the majority of photosensitives, it is the combination of pattern and flickering light, particularly at the lower flash rates, which increases the photosensitive propensity.

8.3. Flashed-Pattern and the Visual Evoked Potential.

As previously mentioned (Section 8.1.), VEP studies involving flashed-pattern or pattern-reversal stimulation have shown that maximal responses are obtained when pattern elements subtend 10' - 30' visual angle, thus indicating receptive field dimensions in the cortex (Spekreijse 1966, Eason et al. 1970, Harter and White 1970; Cigánek 1971; May et al. 1971; Lesèvere and Rémond 1972). The average size of receptive fields was determined to be about 20' (van der Tweel and Spekreijse 1966). However, defocussing the patterned stimuli through diffusers or diopter lenses necessitated larger pattern sizes in order to produce comparable VEP results to those obtained under normal viewing conditions (Harter and White 1968; White 1969; Arden 1973).

It is generally accepted that in man the base of the fovea is approximately 1^{o}, that of the entire foveal depression 5^{o} and that of the combined foveal and parafoveal area about 8^{o} (Polyak 1957). However, VEP mapping over the cortex has shown that the central portions of the visual field have a much larger representation than the peripheral field (Regan 1972). The visual cortex is rich in cells responsive to contour and contrast (Hubel and Wiesel 1959; 1962; 1968) and pattern activates a much greater concentration of neurons, unlike diffuse retinal illumination by white light, which produces antagonistic inhibition and excitation within the receptive fields producing widespread cancellation of their signals. In a similar manner, checkerboard patterns have been found to be effective stimuli for luminance VEPs, rather than gratings, as each square fits into the receptive field centre whereas stripes also illuminate the inhibitory surround. More

cortical channels are therefore stimulated by checkerboard patterns than gratings, which preferentially stimulate one channel (Arden 1973). It follows that the observed increases in VEP amplitude are directly related to the number of spatial frequency channels activated in the cortex (Campbell and Maffei 1970).

A curvilinear relationship appears to exist between element size in a pattern and VEP amplitude, (Spekreijse 1966; Flamm 1974). Discrepancies in the overall visual field of the stimulus therefore seem likely to account for the slight variations in reported optimum pattern size. There is indication that different checkerboard sizes are required for optimal stimulation of different retinal locations (Regan 1972). Harter (1970) reported that comparable responses during foveal and peripheral stimulation could only be achieved if checkerboard size was progressively increased from 7.5' to 60' of visual arc. In accordance with foveal cortical representation and relative positioning near the scalp, the pattern response appears to be generated mainly by the central fovea (Spekreijse 1966; Rietveld et al. 1967; May et al. 1971; White 1974). However, some interindividual differences appear to exist regarding the sudden fall off in VEP amplitude when stimulation has extended beyond central vision. The major part of the evoked response has been reported as occurring within 4^{o} (Andreassi, Okamura and Stein 1975), 5^{o} (Bornstein 1975), 8^{o} (Kooi, Tucker, Danial and Marshall 1972) and 10^{o} (Halliday, McDonald and Mushin 1973) of central retina. Arden (1973) observed that with a checkerboard pattern of 9' square subtense, VEP amplitude increased with increase in screen size up to a 2^{o} visual angle. Beyond this further increase in the overall target had no effect on the evoked potential. It

was illustrated that for a target size of about 7^{o} optimal pattern elements were 18' whereas a larger stimulus of 18^{o} required a square subtense of 35'. Similarly Bornstein (1975) reported that a checkerboard pattern of 26' visual angle within an overall target subtending 8^{o} visual arc mainly generated a foveal response.

On the basis of normative VEP data an experiment was therefore devised to determine the relative effects of macular and peripheral flashed-pattern stimulation on the photosensitive patient.

8.3.1. Laboratory technique and pattern stimuli.

The effect of flashed checkerboard patterns were tested in 8 photosensitive patients, ranging in age from 7 years 11 months to 28 years 1 month, and 8 sex and age matched control subjects (age range 8 years 8 months to 28 years). At the time of investigation, no patient was receiving sodium valproate. However, 3 patients had been prescribed phenobarbitone and 1 patient phenytoin.

Eight circular patterns were superimposed onto the Grass PS22 stroboscope and presented in a random order. The overall stimulus subtended a 25^{o} visual angle which according to the neural representation formula of Drasdo (1977) corresponds to 76% stimulation of visual channel capacity. The patterns were designed for differential but optimal stimulation of the central and peripheral retina. Each pattern consisted of a central disc subtending 12^{o} and an outer annulus with a surface area subtending a 13^{o} visual angle. These dimensions corresponded to a 50% and 53% potential channel capacity respectively. The central and peripheral annuli contained black and white checks of 26' and

1^{o} square subtense and vice versa. In four patterns macular or peripheral stimulation was blacked out and the remaining annulus contained either a 26' or 1^{o} check-size (see Fig. 8.1. a - h). Maximal cortical stimulation theoretically occurred, therefore, during flashed-pattern with 26' checks within the central 12^{o} disc and 1^{o} checks at the outer 13^{o} annulus (Fig. 8.1.e) (Drasdo - personal communication). Stimulus dimensions were obtained by placing the lamp at 29cm from each patient's opened eyes.

The checkerboard patterns were made from print enlargements of a Devices black and white checkerboard photographic slide. The test patterns were transparencies taken of the reconstructed prints. The intensity of the lamp was 1,363 nits. However, superimposition of the patterns reduced light transmission by varying amounts as shown in Fig. 8.1. (a - h).

When assessing the real difference between central and peripheral stimulation, it is important to minimise the effects of fixation and stray light (Rietveld, Tordoir and Duyff, 1965). During testing, patients were instructed to view a small, open fixation point and their direction of gaze was continually monitored. Two methods of reducing retinal stimulation by stray light were proposed by van Balen, van der Gon and Hellendoorn (1966); either a low intensity stimulus can be used, producing minimal stray light or recording should be carried out under background illumination. This would suppress the activity of surrounding receptors when stimulating a localised area of the retina. Unfortunately, the first method requires the averaging of many responses as VEP amplitude would be much lower than the spontaneous activity in the occipital area. This is impracticable with photosensitive

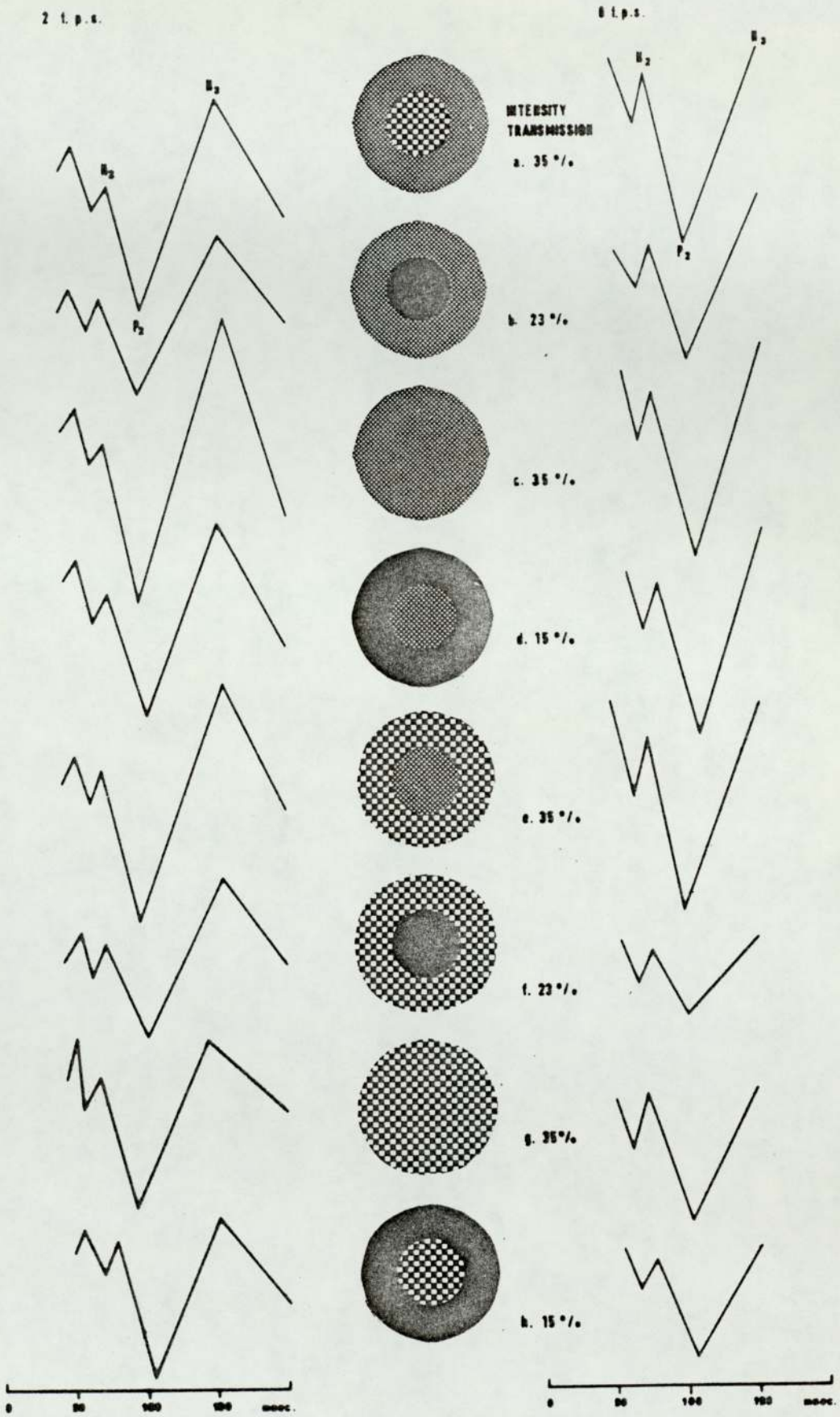


Fig. 8.1. Flashed - Pattern VEPs at 2 and 8 t.p.s. in Photosensitive patients. Mean latencies and amplitudes are plotted for each pattern (a - h).

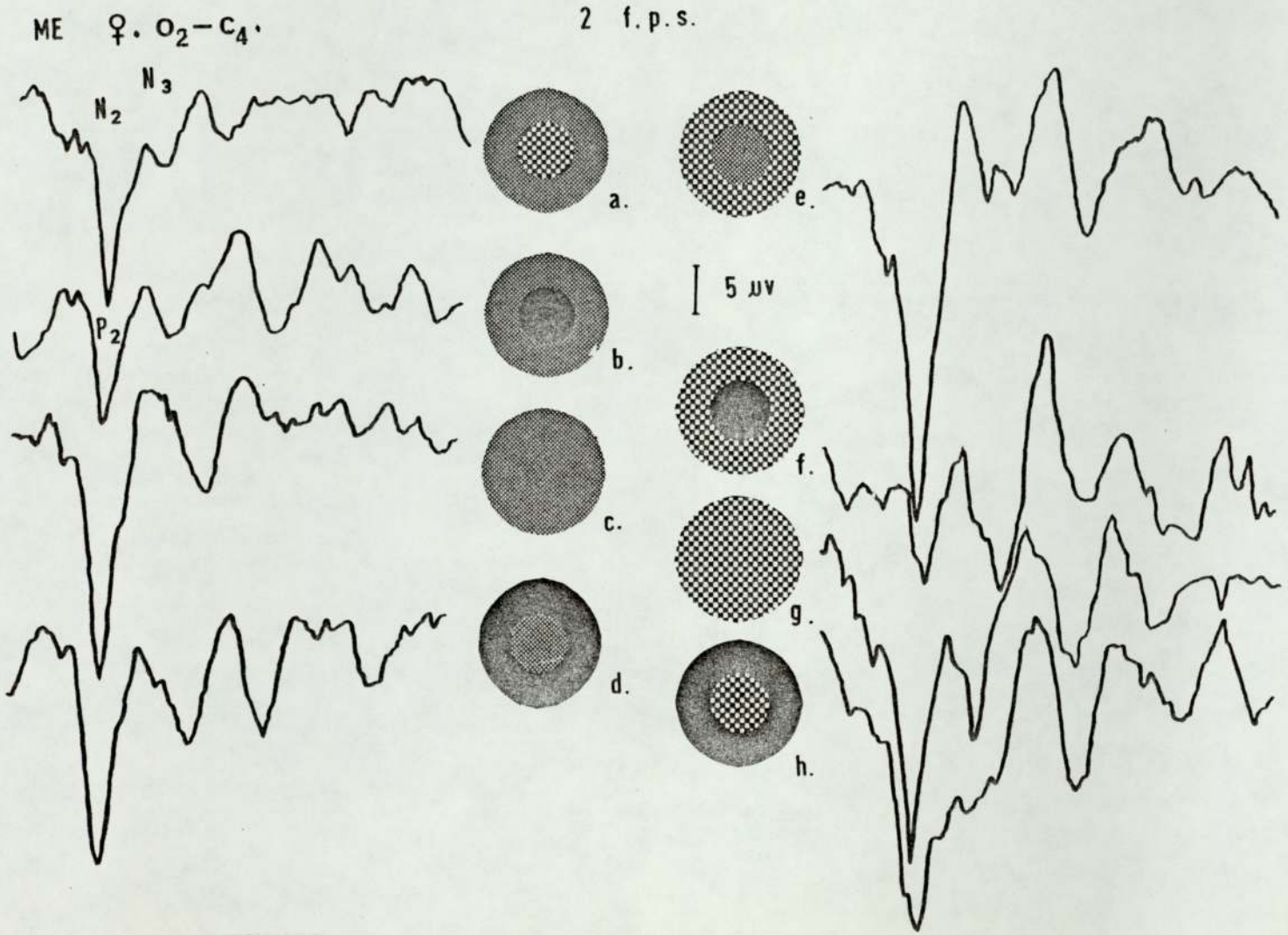


Fig. 8.2. The effect of flashed - pattern on VEP amplitude.

patients due to the increased probability of spike and wave paroxysms during prolonged photic stimulation. A background illumination at an average intensity of 4.6 nits was therefore employed to reduce the effect of stray light and to allow easy accommodation of the stimulus.

The VEP was recorded as described in Section 6.7.1. from a parasaggital montage over the left or right occipitocental derivation (O_1 -C_3; O_2 -C_4), depending on which lay over the non-dominant hemisphere . Averaging of the evoked potential was taken at 2, 4, 6 and 8 f.p.s.. The following results, however, are based on latency and amplitude measurements at 2 and 8 f.p.s..

8.3.2. The visual evoked potential and occipital spike.

Comparisons were made within patients for variations in latency and amplitude of VEP components between patterns. The terminology of components is illustrated in Fig. 6.5. ; N refers to a negative peak and P to a positive trough. Amplitude values are therefore given as peak to trough measurements and vice versa.

No significant differences were found between all 8 patterns for the latencies of N1, P1, N2, P2, and N3 at 2 f.p.s., and neither for N1, P1, N2 and P2 at 8 f.p.s; at this frequency N3 was absent due to truncation of the VEP by the short interstimulus interval (Randomised block design, $P > 0.05$). Amplitudes, however, varied significantly in relation to macular or peripheral stimulation (Randomised block design and Tukey's multiple comparison of means test).

The N1-P1 amplitude was significantly increased in amplitude by stimulation of the macula with the small checks at 26' subtense and simultaneous stimulation of the periphery with checks subtending 1° (Fig. 8.1.e) at 8 f.p.s. At this

frequency, the N1-P1 amplitude was significantly decreased when the macula disc was blacked-out regardless of the check size within the peripheral annulus (Figs.8.1band 8.1f.) (1% level of significance, P = 0.01).

The N2-P2 amplitude at 2 f.p.s. was maximal during flashed-pattern when the entire visual field subtended checks at 26' visual angle (Fig. 8.1c.) and was significantly reduced when only the peripheral retina was stimulated with the large checks subtending 1^{o} (Fig. 8.1f.) (5% level). At 8 f.p.s. this amplitude was significantly increased by all flashed patterns containing 26' within the central disc (Figs.8.1e, -.d, -.c) and was again significantly reduced when macula stimulation was absent and 1^{o} checks were presented at the peripheral annulus (Fig. 8.1f.) (1% level).

Whole field stimulation with 26' checks (Fig.8.1c) evoked significantly large amplitudes of the P2-N3 amplitude at 2 f.p.s. In comparison, significantly reduced amplitudes were associated with lack of macular stimulation, regardless of peripheral checksize and central stimulation by 1^{o} checks where the peripheral annulus was blacked-out (Figs.8.1f, -.b, -.h) (1% level). At 8 f.p.s., the P2-N3 amplitude was significantly increased by macular stimulation with 26' checks (Figs.8.1d.and 8.1e.) and consequently minimal amplitude occurred when the central disc was blacked out and the peripheral annulus contained checks subtending 1^{o} visual angle (Fig. 8.1f.) (5% level).

The N3-P3 amplitude at 2 f.p.s. was maximised significantly by flashed-pattern with the 26' checks in the entire visual field (Fig. 8.1c.). This amplitude was significantly diminished when either the central disc was blacked-out,

regardless of check size at the periphery (Figs.8.1f and 8.1b), or when only large checks were situated at the macular or within the whole visual field (Figs.8.1h and 8.1g)(1% level).

No significant differences were found between patients and controls as regards the latencies of all VEP components at 2 and 8 f.p.s. for all patterns (Two-way analyses of variance, $P > 0.05$). However, amplitudes were significantly greater in patients for N1-P1 at 8 f.p.s. (1% level); N2-P2 both at 2 and 8 f.p.s. (1% level); and N3-P3 at 2 f.p.s. (1% level). The P2-N3 amplitude at 2 and 8 f.p.s. was significantly increased in photosensitives at its maximal amplitude but no significant differences were seen between patients and controls at the minimum amplitude of P2-N3, i.e. in the absence of macular stimulation.

The Two-way analyses of variance showed no significant interaction between the patterns and both subject groups as regards latency or amplitude of all components ($P > 0.05$). This meant that although VEP amplitudes in normal controls were significantly reduced in comparison to those seen in photosensitives , amplitude variations between flashed patterns followed a similar trend in patients and controls.

In conclusion, no significant differences were found within patients or between patients and controls for VEP latency variations between whole field, macular, or peripheral stimulation of the retina by flashed-pattern. Amplitude measurements were, however, significant at the 1% level for P2-N3 and N3-P3 at 2 f.p.s., N1-P1 and N2-P2 at 8 f.p.s.; at the 5% level for N2-P2 at 2 f.p.s. and P2-N3 at 8 f.p.s. This meant that a consistent and significant variation existed in the overall amplitude of the major positive component (P2) which was

significantly increased by stimulation of 12° of central retina, with small black and white checks of 26' subtense regardless of peripheral stimulation, and was significantly reduced in the absence of macula stimulation, even when optimal stimulation of the peripheral retina with 1° checks was presented, despite the fact that both retinal locations potentially stimulated half of the visual channel capacity.

Similar tests could not be conducted for latencies and amplitudes of the occipital spike as only 4 of the 8 patients showed this abnormality, and then only in relation to the type of flashed-pattern stimulation. Analysis of occipital spike distribution revealed that the probability of IPS at 8 f.p.s. evoking occipital spikes differed significantly in relation to the type of pattern (Cochran Q test, $Q = 14.66$ df 7, $P = 0.05$). Occipital spikes were not observed during IPS where macular stimulation had been blacked-out, and the peripheral annulus consisted of large 1° checks, or when these large squares were presented over the entire visual field. Occipital spikes occurred in all 4 patients during whole field IPS with small checks at 26' subtense.

To summarise, the greatest response of the VEP at 2 and 8 f.p.s. appears to be directly related to optimal stimulation of the macula and is most evident in the overall amplitude of P2. This suggests that this major inhibitory wave is related to macula functioning and to photopic systems initiated by cone activity in this rod-free area. Such findings are in agreement with Gastaut et al. (1966). Lehtonen (1973) observed that the N2-P2-N3 sequence was particularly sensitive to the field size of a contoured stimulus and proposed that even late VEP deflections at the occiput

reflected the function of a modality specific cortical area. In the present study, the above response was significantly greater in photosensitives and, as there was definite indication that occipital spikes in the VEP were similarly related to macular stimulation, if the overall P2 wave is modality specific, this implies an instrumental hyperexcitability of the primary projection area in photosensitives. However, there is some disagreement in the literature as to the specific versus non-specific modality of VEP components (Cigánek 1961; Kooi and Bagchi 1964; Gastaut and Regis, 1964; Spehlman 1965; Bergamini and Bergamasco 1967; Creutzfeldt and Kuhnt 1967), and this is discussed in Section 9.2.2. in relation to both the effect of pattern and sodium valproate on the photosensitive VEP.

9. Discussion.

9.1. Efficacy of Sodium Valproate on Photosensitivity

Prior to the study of the therapeutic effects of sodium valproate on photosensitivity it was essential to establish valid and reliable parameters that defined the photoconvulsive propensity. The most provocative flash frequencies for evoking PCRs have repeatedly been reported as occurring between 10 - 20 f.p.s. although wide individual differences may exist in overall sensitivity ranges (see Section 1.8). Adopting a provocative and standardised IPS technique, investigation of 167 photosensitive patients over 12 years showed that the peak lower limit of sensitivity was at 8 f.p.s., whereas a bimodal peak occurred for the upper limit at 16 - 20 f.p.s. and 46- 50 f.p.s., indicating that a narrow or wide sensitivity range was possible. This is in agreement with Jeavons and Harding (1975). However, both the lower and upper limits showed close repeatability within a 3 -month period. Although the deviation in actual flash rate of the upper limit was usually greater than that of the lower limit, the reverse was true when considering the inter-stimulus interval. Nevertheless, it became obvious that variation in both limits followed a similar trend when percentage deviation was considered and that the lower and upper limits were reliable measures of the photosensitivity range.

There has been some discussion in the literature as to the effects of standard anticonvulsants on photosensitivity. Varying success has been reported but usually only in conjunction with other precautions, e.g. polarised sunglasses (Pantelakis et al. 1962). Long-term treatment of photosensitive epileptics with clonazepam was reported by Rail (1973) and Hooshmand and Oliver (1975) who recommended clona-

zepam as the first drug of choice for this condition. However, this drug may produce various adverse side-effects and may cause onset of tonic-clonic seizures for the first time in some patients. Photosensitive epilepsy has been found to be very resistant to anticonvulsant medication (Livingston 1964; Troupin 1966). In the present study, standard antiepileptic drugs were found to have had no beneficial effect on the photosensitivity range before sodium valproate treatment.

The population of photosensitive patients from which a sample was drawn for sodium valproate therapy was predominated by females (ratio 100: 185) which supports the findings of Herrlin (1954); Watson and Marcus (1962); Wadlington and Riley (1965); Doose et al. (1969a, b); Jeavons and Harding (1975). The mean age of patients was 13 years 6 months and about half the pstients (51%) had a clinical history of fits purely in response to flickering lights (Group I). As in other studies (Charlton and Hoefer 1964; Wadlington and Riley 1965; Hishikawa et al. 1967; Doose et al. 1969b; Lopez 1973; Jeavons and Harding 1975) the most common clinical seizure was a tonic-clonic fit (65%) with the highest incidence occurring in Group I (42%). It was concluded that if photosensitivity could be successfully treated, at least two-thirds of patients would probably be controlled for major generalised epilepsy.

9.1.1. EEG studies.

Fifty photosensitive patients, ranging in age from 6 - 25 years, were treated with sodium valproate but, before introduction of this drug, all patients received at least one pre-drug EEG investigation. Of the 23 patients who had previously been receiving other anticonvulsants, 11 continued to take reduced dosages of usually one drug during sodium

valproate treatment. Sodium valproate was introduced gradually and subsequent dosage increases were determined by regular EEG follow-ups.

Many photosensitives may show normal basic EEGs particularly those in Group I. However, about 54% of all patients show some EEG abnormality in the absence of photic stimulation (Jeavons and Harding 1975). In the present study, the EEG was recorded using standardised techniques (see Section 6.3), then analysed visually and by period analysis. Of the 50 patients, 72% had some degree of abnormality in their basic EEG before treatment. The most frequent types of abnormality were generalised atypical 3 c.p.s. spike and wave (29.2%) or polyspike and slow wave complexes (29.2%). The former has previously been considered as the most common type of spontaneous abnormality (Bickford et al. 1953; Capron 1966). Localised abnormalities were less common (25%) and usually occurred as occipital spikes or sharp waves. About 25% of patients exhibited abnormalities immediately after eye-closure.

Sodium valproate proved to be extremely effective in removing spontaneous EEG abnormalities. Even at a low dosage of 800 mg/day alone, significant improvement was evident in the persistency and amplitude of abnormality. Although at all dosages of sodium valproate, it was possible to see spontaneous discharge similar to that occurring before treatment, it appeared in a much reduced form. Complexes containing slow waves were particularly responsive to treatment and the evocative effect of eye-closure appeared dose-dependent.

The modal dosage for total basic EEG normalisation

was 1000 mg/day. Overall two-thirds of patients with some form of abnormal EEG prior to sodium valproate became normalised at some point during treatment. This interval ranged from 1 month up to 2 years 4 months, with a mean period of about 8 months, but it was significant that on average patients acquired basic EEG normalisation 4·5 months before a significant improvement in photosensitivity and usually at a lower dosage of sodium valproate. Obviously, assessment of sodium valproate effects was related to the frequency of EEG follow-up which varied between 1 - 3 months and it is possible, therefore, that improvement could have appeared earlier through more frequent follow-ups and quicker increases in dosage. Basic record effects were highly stable and in only 2 patients was continued treatment accompanied by a relapse of the normal EEG with the addition of non-specific abnormality. Withdrawal of sodium valproate brought a speedy return to pre-drug levels of abnormality within an average period of about 3 months.

No adverse interactions were evident in the EEG between sodium valproate and other anticonvulsants, and these drugs (see Section 6.2) exerted no influence over the effects of sodium valproate on the EEG. The results are in agreement with other authors in that sodium valproate was effective in the treatment of generalised bilaterally synchronous 3 c.p.s. spike and wave activity (Fau and Garrel 1968; Mairlot 1970; Völzke and Doose 1973; Jeavons and Maheshwari 1974). However, generalised polyspike and wave of varying frequency was also responsive to this drug. Focal abnormalities, e.g. sharp waves, do not usually seem to be affected by sodium valproate unless bilateral spike and wave abnormalities are also present

in the EEG (Völzke and Doose 1973). Comparison is difficult, as in the present study only 1 out of the 29 patients analysed in detail had purely localised bilateral occipital sharp waves which, in fact, diaappeared by 800 mg/day. When comparing the modal dosage of 1000 mgm. with pre-drug findings, it was evident that whereas reduction in generalised atypical spike and wave had occurred by a factor of 57% and similarly polyspike and wave by 71%, only a 33% reduction had occurred in localised spiking. Both patients with rolandic spikes and 2 out of 4 patients previously with occipital spikes kept them throughout valproate treatment.

Period analysis was used to determine alterations in background activity in photosensitive subjects before, during and after sodium valproate therapy, and comparisons were also made with age and sex matched controls. In patients not receiving anticonvulsants prior to sodium valproate, the resting (pre-hyperventilation) EEG contained significantly more alpha activity than in control subjects. Although there is evidence to suggest a reduced alpha response at a first EEG recording (Johnson and Ulett 1959), this does not explain why at optimum dosage patients' EEGs now showed significantly less alpha activity than in normal controls. Within patient comparisons indicated that, in fact, neither the total EEG index nor the occurrence of any specific waveform had been significantly altered by sodium valproate treatment, although theta activity had increased slightly at optimum dosage. Miribel and Marinier (1968) reported a slowing down of rhythms during sodium valproate treatment. Hyperventilation records showed no significant differences between patients and controls or between all levels of sodium

valproate treatment within patients. These results are consistent with the findings of Fau and Garrel (1968) and De Biolley and Sorel (1969a, b) who also found no changes in background EEG rhythms in sodium valproate treated epileptics. However, period analysis fails to register amplitude changes which usually occur during hyperventilation. In agreement with Miribel and Marinier (1968) sodium valproate was characterised by a lack of LVFA as seen with other drugs, viz. barbiturates. However, after withdrawal of sodium valproate, beta activity was greatly increased in patients and was not the result of additional medication. Patients who retained abnormal EEGs during treatment showed no significant effects on background activity, which is contrary to the suggestion of Miribel and Marinier (1968) that any changes in the background EEG are constant in all patients and independent of reduced spike and wave activity.

Although the photosensitives were predominantly female, sodium valproate was found to have no differential effect on the basic EEG between the two sexes and neither was there any indication of the drug's effectiveness being influenced by hormones of the menstrual cycle. Prior to treatment, the incidence of abnormal EEGs was significantly greater in those patients with spontaneous seizures (with or without additional photosensitive fits) than patients purely clinically photosensitive. However, sodium valproate had no differential effect on the basic EEG in relation to the standard clinical grouping and in all groups a significant movement occurred towards normalisation of basic EEG activity within a similar time period. The rate of EEG normalisation was also similar between groups in relation to the attainment of a significant

improvement in photosensitivity and neither was there disparity between patients with generalised, minor or mixed seizures.

9.1.2. Effect on photosensitivity.

In agreement with Jeavons and Harding (1975) the most provocative stimulus for the majority of photosensitives was found to be the fine grid flashed-pattern. The differential effect of pattern was, however, more striking at low flash rates and the precipitation of PCRs by occipital spikes varied significantly at the lower limit of the sensitivity range. Occipital spikes were more frequent with the grid pattern flash than diffuse light and therefore light intensity was less crucial than the effect of pattern. At the faster frequencies, it was the flickering light per se which determined the upper limit of the photosensitive propensity. It is suggested that those photosensitives with activation only to or particularly to diffuse flash generally do not have an epileptic condition or begin epilepsy after childhood, lessening the probability of a functional hyperexcitability of visual neurons.

The effect of sodium valproate on photosensitivity in 50 patients was tested under standardised conditions using provocative IPS of diffuse high intensity light combined with a grid pattern of individual squares subtending 26' visual angle, that potentially stimulated 75% of the visual information channels. Before treatment it was established that for a significant improvement to occur in photosensitivity the sensitivity range had to be reduced by at least 78%. Sodium valproate was introduced gradually and follow-up EEGs showed that the time taken to reach optimum dosage, i.e. the

first EEG to show maximal reduction in photosensitivity varied between 1 month to 2 years 9 months, with an average time interval of approximately 9 months.

Few authors have commented on the effect of sodium valproate on photosensitivity (Miribel and Marinier 1968; Völzke and Doose 1973), but it has been noted that effects on photosensitivity are delayed in comparison to EEG and clinical improvement which is supported by the present results. However, it was highly significant that 54% of patients achieved total abolition of photosensitivity, a further 24% significant improvement, and only 22% showed no marked benefit from sodium valproate therapy at the time of study. Therefore, photosensitivity was at least significantly improved in 78% of patients as a direct result of sodium valproate. Optimum dosage ranged from 600 - 1600 mgm. but modal dosage (52%) was 1000 mg/day. Although duration of treatment, age and actual dosage (mg/day) did not vary significantly between improved and unimproved patients, in relation to body weight, dosage was significantly greater (mean, 23.62 mg/kg/day) in the improved patients than in unsuccessful patients (mean, 17.41 mg/kg/day). The range of effective sodium valproate dose levels in children (17.35 - 38.46 mg/kg/day) and adults (1000 - 1600 mg/day) are in close agreement with the trends generally reported for epileptic patients (Fau and Garrel 1968; De Biolley and Sorel 1969a; Dumon-Radermecker 1969; Reckitt and Coleman 1973; Olve et al. 1969; Espir et al. 1975), and also indicates that patients have a somewhat idiosyncratic build-up of sodium valproate levels to optimum dosage. Even at 800 mgm. of sodium valproate a real effect was observed on the sensitivity range which continued up to 1200 mg/day.

After this, any additional overall benefit was slight and these higher doses were usually required by adults with a tendency to be overweight. The reduction in the sensitivity range was mainly due to the lowering of the upper limit so that increasing insensitivity was primarily seen at the higher flash frequencies. However, although the response of the lower limit was slower, the number of patients showing improvement at the low flash rates gradually increased with increased dosage. It was significant that more patients were cured of their photosensitivity while taking sodium valproate than generally occurs spontaneously, and also within a significantly shorter time. This was particularly due to the pure clinically photosensitive patients showing a better prospect of total cure with the treatment than normally demonstrated.

Continued treatment after reaching optimum dosage showed that the beneficial effects of sodium valproate on photosensitivity, as with the basic EEG, were stable. It was notable that the 3 patients who did show a relapse in sensitivity, particular at the lower limit, all had occipital spike precipitation of the PCR. The general effect of terminating sodium valproate was either a reappearance of the PCR, where this had been abolished, or an increase in photosensitivity, where it had remained during treatment. From the 16 patients withdrawn from sodium valproate, it was evident that a continuing, but gradually decreasing, effect of the drug existed on the fast flash frequencies as, after 3 months a further deterioration had occurred in the upper limit. The lower limit relapsed within 1-3 months after withdrawal.

Several authors have commented on the lack of

similarity in some cases between spontaneous EEG paroxysms and those evoked by IPS in the same patient (Hutt et al. 1963; Hishikawa et al. 1967). In the present study, both similar and different responses were found but, whereas approximately 30% of patients exhibited spontaneous polyspike and slow wave or atypical spike and slow wave complexes respectively, PCRs mostly took the form of generalised polyspike and slow waves of varying frequency (82%), followed by atypical 3 c.p.s. spike and wave discharge (44%). However, 52% of patients showed more than one type of PCR and it was noted that the amount of slow wave component tended to increase with longer flash durations.

The sensitivity range and the nature of the PCR have been suggested as useful therapeutic measures (Jeavons and Harding 1975). As previously mentioned, increase in sodium valproate was accompanied by a decrease in PCR appearance, particularly at the higher frequencies. However, before disappearance the PCR was usually replaced by degraded forms of the response. Even at a low dosage, sodium valproate began to detensify the PCR and towards optimum dosage a significant reduction was seen in persistency and amplitude, together with a delayed onset of photically evoked abnormality. The most common form of degraded response was ill-defined PCRs with poor frontal extension; maximal in the occipital derivations. Although IPS was presented, with patients' eyes-open and eye-closure was not tested, abnormality readily evoked by eye-blinks in the untreated patient was far less common during sodium valproate therapy. Although drug withdrawal caused a return to pre-drug levels, except for the continuing but temporary effect on the upper limit, it was noted that within 3 months after cessation of sodium valproate,

despite a quantitative return of the sensitivity range, the critical frequencies were slightly more inconsistent compared to pre-drug levels which is attributed to the increased occurrence of on-, off- and mid-responses (93% of patients) after sodium valproate therapy than previously seen before treatment (67%).

As with the basic EEG, sodium valproate showed no differential effects on photosensitivity between males and females nor was its effectiveness in females influenced by the menstrual cycle. Although as previously mentioned, clinically flicker-sensitive epileptics (Group I) were more likely to be cured while receiving sodium valproate, the drug was equally as effective in producing a significant improvement in all 3 clinical groups.

The incidence of occipital spikes in the EEG of the overall photosensitive population was 51%. This was not influenced by either sex, clinical grouping or seizure type (i.e. generalised, minor or mixed seizures). In the 50 patients treated with sodium valproate, 25% showed occipital spikes in their pre-drug basic EEGs compared to 65.5% during IPS. Hishikawa et al. (1967) also found that resting EEG patterns were not indicative of whether PCRs were precipitated by occipital spikes or appeared simultaneously over all areas. During sodium valproate treatment it was evident that even high dosages had no appreciable effect on occipital spikes. However, it was significant that occipital spikes remained, even after total disappearance of the PCR, in those patients with persistent occipital spikes at low flash rates, rather than in those patients where the PCR had previously been triggered by a brief occipital spike abnormality. This

supports the findings from the basic record that localised spiking was the most resistant form of abnormality to sodium valproate therapy.

Although the standard clinical groups showed a similar incidence of occipital spikes before and during treatment, significantly more patients sensitive to television, regardless of whether fits also occurred spontaneously, were found to have occipital spikes prior to treatment than non-television sensitive patients. It is interesting that Darby et al. (1977) found a significant relationship between spike and wave discharge to pattern-movement and television fits. As occipital spikes have been shown to be related to the presence of pattern, there appears to be a definite link between 'television epilepsy' and initiation of paroxysms by localised occipital spikes. No clinical difference was found, however, between patients who lost or retained occipital spikes and likewise between both sexes. Although Völzke and Doose (1973) found an increase in spontaneous focal abnormality in some epileptics treated with sodium valproate, in the present study no increase was observed in occipital spikes as a result of treatment.

9.1.3. The visual evoked potential.

Flash VEP data was obtained on 25 patients and matched controls using a similar recording method as when determining photosensitivity. Latencies and amplitudes of components, defined by a negative (N) or positive (P) polarity and numerical subscript, were measured at 1, 7 and 9 f.p.s. for the potential recorded over the non-dominant hemisphere. Due to the discrepancies among epileptic VEP studies and the confounding effects of spike and wave (Gastaut and Régis 1964; Rodin et al. 1966; Chatrian et al. 1970b) recording before and after treatment was made using short, intermittent runs of flashes

at the faster frequencies to avoid contamination of the VEP with generalised abnormalities. Before sodium valproate treatment, no significant differences were found between patients on standard anticonvulsants and those not receiving medication as regards latencies and amplitudes. At optimum dosage of sodium valproate only 2 patients were receiving reduced dosages of other drugs.

Prior to commencing sodium valproate, photosensitive VEPs at 1 f.p.s. showed no significant differences from control VEPs in latency of all components. However, amplitude was significantly larger in photosensitives (1% level) which was mainly due to the increased overall amplitude of P2 (N2 - P2 and P2 - N3) at around 106 msec. and on average 20-42 μv. Although sodium valproate had an appreciable affect on the amplitude of this component (1% level), it was still greater in patients than in controls, even though a significant reduction had occurred in the photosensitive response. The effect of sodium valproate was still evident to some extent (5% level) after withdrawal and, in fact, VEP amplitude was similar between both patients and control subjects. The VEP at 7 and 9 f.p.s. did not differ significantly between these two groups or within patients at any stage of treatment. However, P2 amplitude at optimum dosage and after withdrawal of sodium valproate tended to be of greater amplitude in photosensitives and it is suggested that the overall lack of significance at these faster frequencies was due to the use of intermittent brief trains of flashes which did not permit a buildup of amplitude in photosensitive patients.

The frequency of occipital spikes in the VEP was 50%

at 7 f.p.s. and 16% at 1 f.p.s.. These are much lower incidences than previously reported (Panayiotopoulos et al. 1972; Dimitrakoudi et al. 1973), even though a highly provocative flash stimulus was used. It is suggested that in the absence of comparisons with normal controls the large amplitude N2 component (N2 - P2) might be mistaken for an occipital spike at 1 f.p.s., although in 3 patients the spike at 7 and 9 f.p.s. was due to definite enhancement of the N2 component. An overall latency relationship was found between the triphasic P2ab component and the occipital spike, particularly the negative polarity, and therefore supports the findings of Dimitrakoudi et al.(1973) and Jeavons and Harding (1975), Both types of component were commonly seen on the descending arm or base of P2 and, although the P2ab wave was an infrequent but normal occurrence in controls at the faster VEP frequencies, it was significantly more common in the photosensitive VEP at 1 f.p.s.. The negative polarity of P2ab on average ranged from 93 - 113 msec. and that of the occipital spike 84 - 100 msec.. Neither component was significantly affected in latency or amplitude by sodium valproate.

The photosensitive VEP was further investigated using flashed-pattern checkerboard stimuli which selectively stimulated the macula area (12^{o} visual angle) and peripheral retina (13^{o}) with small checks at 26' and large checks at 1^{o} visual angle. No significant variations were found in latency of all VEP components at 1 and 8 f.p.s. between patients and controls, or for patients between VEPs evoked from stimulation of the different retinal locations. However, a significant and consistent variation was found in the overall amplitude of P2 (N2 - P2 - N3 sequence) and also for the late

deflection N3 - P3 at 2 f.p.s. and the early deflection N1 - P1 at 8 f.p.s. which were significantly increased by stimulating the 12° angle of central retina with small black and white checks of 26' subtense, regardless of peripheral stimulation. Amplitudes were significantly diminished when macular stimulation was blacked out or also, in the case of P2 - N3 and N3 - P3 at 2 f.p.s., contained the 1° checks.

Even though central and peripheral stimulation both potentially stimulated 50% of the visual information capacity, it was evident that optimal stimulation of the macular evoked the largest amplitudes, particularly of the P2 component, in both patients and controls. However, the amplitude was significantly increased in photosensitivies (1% level). The frequency of occipital spikes at 8 f.p.s. in photosensitive patients was similarly related to macular stimulation. These results, therefore, agree with those of Chatrian et al. (1970a) who found marked epileptogenic effects with patterned stimulation of the macular in contrast to the futile stimulation of peripheral retina in pattern-sensitive epileptics, and supports Jeavons et al. (1972a) who reported that suppression of abnormal responses occurred when photosensitives shifted their direction of gaze away from the centre of the lamp and during lateral photic stimulation.

9.1.4. Clinical findings.

The clinical histories of the 50 photosensitive patients showed that the most common form of seizure, whether occurring alone or associated with other fits, was a tonic-clonic convulsion (86%). Absence seizures occurred in 20% and myoclonic jerks in 14% of patients. Partial seizures were the most infrequent (10%) clinical manifestation.

However, no significant differences were found between seizure-types in the effects of sodium valproate on the basic EEG or photosensitivity, as the majority of patients had generalised abnormality alone or in combination with localised abnormalities which have been reported to show greater response to treatment than purely focal abnormality (Völzke and Doose 1973).

As the majority of patients (76%) had suffered epileptic attacks in direct response to flicker stimulation, it was not possible to assess sodium valproate improvement on precise clinical criteria, i.e. reduction in fit frequency. However, benefit on seizures was noted as withdrawal of sodium valproate caused a return of clinical photosensitivity and tonic-clonic fits in a few cases besides spontaneous myoclonic jerks and eyelid myoclonia. These types of seizures have previously been reported to respond well to sodium valproate treatment (see Section 4.11.). Patients impulsively attracted to the television before therapy were greatly improved by sodium valproate, even when only a small reduction was observed in the sensitivity range. Withdrawal of the drug proved that loss of attraction had been due to the direct action of valproate, as patients again experienced this impulsive sensation.

There were no patients who self-induced attacks by eye-blinking, etc. in this sample but, due to the effect of sodium valproate on impulsive attraction to television, eyelid myoclonia in the mornings or in sunlight, spontaneous and photically induced abnormality particularly by eye-closure and eye-blinking, and clinical seizures, this drug might prove to be extremely useful for this form of resistant epilepsy. Simil-

arly, these patients are known to have behavioural problems and school performance is poor. In the present study, sodium valproate allowed children to lead less restricted lives and many had feelings of wellbeing whilst receiving the drug. Only 1 patient experienced adverse sensations of tiredness and lapses in memory, which was probably due to her combined medication with ethosuximide and phenobarbitone creating increased serum levels of the latter drug, known to occur in this situation (Haigh and Forsyth 1975; Harwood and Harvey 1975).

9.1.5. Contraindications.

Overall, 16% of patients showed definite evidence of side-effects as a result of sodium valproate. The most common ailment was stomach upset (17%), which was minor and transient in several cases. However, in 10% of patients this complaint was severe. Curly hair was seen in 8% where all but one patient were taking sodium valproate alone. Changes in appetite were believed to be idiosyncratic effects and, of the 7 patients actually reporting an increase in weight, 5 were female. Overall, no significant affects on weight changes were found from sodium valproate treatment. There was some suggestion that migraine might be aggravated in susceptible cases. No conclusive evidence was found for contraindications of sodium valproate with the contraceptive pill or during pregnancy, although amenorrhea occurred in one female patient receiving 1000 mg/day of sodium valproate and Gynovolar, where seizures had previously coincided with menstruation.

9.2. Pathophysiology of Photosensitivity.

9.2.1. Thalamo-cortical visual pathways.

Before an understanding can be reached of the physiological mechanisms underlying photosensitivity through clinical and experimental study, it is necessary to know how visual information is processed by the brain and the relationship between sub-cortical and cortical functions. The optic fibres pass from retinal receptive cells, cross over in the optic chiasma and extend through the lateral geniculate nuclei in the thalamus. This optic tract spreads fanlike (optic radiation) within the temporal region of the cortex and terminates at the primary projection area of the striatal occipital cortex (Smith 1970; Luria 1973). It is therefore possible that a dysfunction giving rise to photically induced seizures could exist at the retina, lateral geniculate body or cortex. However, the maintenance and regulation of cortical tone, which is essential for organised mental activity, actually operates in the subcortex and brain stem which, in turn, undergo regulatory influence from the cortex (Luria 1973). A defect in these sub-cortical systems might also be operating in photosensitive epilepsy.

Sub-cortical systems can broadly be considered as regulating sensory afferent input and efferent output of the cortex. Two basic systems have been identified. A diffuse non-specific thalamo-cortical mechanism for internal inhibition, capable of modifying partially or totally sensory, motor and higher functions (Morison and Dempsey 1942; Jasper 1949; Himwich 1961). The reticular system, or nerve net, in which are connected short-axoned nerve cells over which excitation spreads, not as isolated impulses according to an 'all or

nothing' law but gradually, changing its level little by little and so modulating the whole state of the nervous system (Moruzzi and Magoun 1949; Magoun 1958; Luria 1973). The reticular system is divided into the activating ascending reticular system (ARAS) extending upwards through the thalamus, caudate nucleus, limbic system and finally the neocortex. Other fibres run in the opposite direction through these structures and pass down to lower regions in the mesencephalon, hypothalamus and brain stem. This pathway is called the descending reticular system (DRS) and controls autonomic reactions and movement. The ARAS and diffuse thalamocortical fibres supposedly interact in regulating ascending sensory input and the sleep-wakefulness cycle (Jasper 1949; Magoun 1958). A feedback relationship therefore exists between the thalamic-reticular system and cortex.

The early assumption that the diffuse thalamic-reticular system was solely a non-specific means of inhibition and activation is, however, an overstatement (Luria 1973; Kaplan 1974). Besides sensory impulses ascending the primary projection pathways, collateral fibres pass from these classical sensory tracts to the reticular system, ascend in that structure and impinge upon the unspecific regions. By an alternate pathway the ARAS sends fibres by topographical arrangement directly to the cortex without stoppage in the thalamus (Jasper 1949). It is proposed that the direct pathway alerts the cortex while the diffuse thalamic system modifies inhibition (Himwich 1961).

The thalamo-reticular system has therefore an homeostatic function promoting stability and preventing brain overactivity. Modulatory influences have been detected within

each major sensory system (Magoun 1958), e.g. projections to and from the parietal-occipital cortex exist in the thalamic-reticular system.

Another important cortical relay is the limbic system which connects the old cortex, rhinencephalon, with the neocortex and is thought to integrate the rudimentary awareness of the former with the discriminatory consciousness of the neo-cortex. The connections have been termed the 'hippocampal ring' or Papez circuit (Luria 1973; Himwich 1961), linking the hippocampus, fornix, hypothalamus, anterior thalamic nuclei, cingulate gyrus and cortex. The circuit is completed by fibres leaving the cingulate gyrus and returning to the hippocampus. It is known that the rhinencephalon is more susceptible to seizures than the neocortex. Lesions in the hippocamous disturb memory functions (Luria 1973) and the circuit also modulates emotional activities of the hypothalamus (Himwich 1961). The hypothalamus is therefore functionally linked to the limbic structures and ARAS, and similarly a close relationship exists between the limbic cortex and the reticular system.

9.2.2. Centrencephalic versus focal mechanisms.

The majority of photically induced clinical seizures have been shown to be generalised and, in particular, take the form of primary generalised tonic-clonic convulsions. The concept of the mechanism for generalised seizures is that the fit is triggered either from the brain stem reticular formation, due to a lowered seizure threshold, or that it is triggered from the central system by spread from a focal cortical lesion, which may go undetected by EEG examination (Schmidt and Wilder 1968). A higher incidence of PCRs is usually found in

primary generalised, or centrencephalic, epilepsy (Melsen 1959; Doose et al. 1969b), which is predictable due to the frequent, bilaterally synchronous 3 c.p.s. spike and wave PCR (Jeavons and Harding 1975). However, some believe that all epilepsy has a focalised origin (Alström 1950; Aird 1970) and, in the case of photosensitive epilepsy, there has been much controversy as to the relative importance of focal and/or subcortical mechanisms.

ERG studies and IPS using coloured lights led to conjecture about the role of the retina in photosensitivity (Brausch and Ferguson 1965; Capron 1966). Similarly, Green (1969) implicated the retina after finding an early positive ERG wave during IPS at 9 - 15 f.p.s., which also evoked EEG seizure discharge. This early wave was enhanced by red light and augmented or activated by eyeclosure. However, although ERG amplitude increased during photically induced spike and wave, it was not apparently fundamental to photosensitivity itself but depended upon the incidence of cerebral paroxysmal activity. He therefore proposed that a failure of inhibitory mechanisms existed at all levels and that retinal elements were released from higher control a seizure, so that propagation of the attack might result from intensified or distorted input. In the reticular system, centrifugal effects have been observed on trigeminal and cochlear nuclei and also retinal activity (Magoun 1958). Hishikawa et al. (1967) were, however, unable to find any significant differences between the ERGs of photosensitive epileptics and normal subjects, although it is notable that they used only single and double flashes.

Many authors have commented on the provocative effect of eye-closure in evoking seizure discharge, particularly

during IPS, and several theories have been proposed (Bickford et al. 1953; Atzev 1962; Jeavons 1966; Green 1968). Bickford et al. (1952) suggested that PMR mechanism and eyeclosure affects on the PCR were due to feedback mechanisms from the frontal muscles facilitating impulses from the eye at a locus in the reticular system. However, with eyeclosure it is only sudden voluntary movement that involves not only a contraction of the orbicularis oculi muscles, causing an upward roll of the eyeballs, but also pupillary constriction despite the concomitant reduction in light intensity (Brazier 1953). In contrast, with gentle eyeclosure the upward roll does not occur and the pupils dilate. This is interesting, as the effects of eyeclosure on the spontaneous EEG can differ. Eyeclosure in total darkness may produce EEG activation but only with voluntary movement when the eyeball was seen to roll definitely upward (Green 1966). Slow, passive eyeclosure, under normal illumination, on the other hand, has failed to produce spike and wave discharge (Panayiotopoulos 1974). Proprioreception, therefore, appears to be definitely implicated. As previously mentioned, interconnection exists in the brain stem between the facial and trigeminal nerves and the reticular system which influences afferent transmission in these neurons (Magoun 1958). Similarly, eyeball-rolling and pupil constriction can be evoked by electrical stimulation of the central tegmentum fasciculus and ventral and caudal regions of the pons; also reticular feedback control of retinal discharge is known to occur by modification of the pupillary hole (Naquet et al. 1960). Eyeclosure has been proposed to lower cortical tone (Atzev 1962) and in a suspected diagnosis of photosensitive epilepsy the appearance of eyeclosure evoked

abnormality in the spontaneous EEG is virtually indicative of subsequent photically induced spike and wave (Jeavons and Harding 1975). It is therefore relevant that in the present study sodium valproate was effective in abolishing both spontaneous eyeclosure activation and that evoked by eyeblinks during IPS (as dosage was increased) which may be an initial indication of this drug's effect on the thalamic-reticular system.

Various spontaneous and experimentally-induced rhythms can be detected in the centrencephalic systems. Activation of certain regions of the thalamo-cortical pathway produces a slow wave response which, when linked to stimulation of the reticular system, results in spike and wave, (Jasper 1949). Surgical section of the fornix (part of the limbic system) prevents spread of this discharge to parieto-occipital areas. Early studies compared this induced spike and wave in animals to that seen in absence seizures, in which the primary symptom was loss of consciousness (Morison and Dempsey 1942). The spread of abnormality from one cortical region to another appeared to be from the thalamus itself, rather than trans-cortically. Although minor absences are not as common as tonic-clonic seizures in photosensitive epilepsy (see Section 1.5), as noted in the present study, during IPS the most frequent type of seizure when evoked is an absence with associated typical or atypical 3 c.p.s. spike and wave activity (Bick-ford et al. 1952; Melsen 1959; Jeavons 1969; Jeavons and Harding 1975). Sodium valproate appears now to be the first drug of choice for absence seizures (see Section 4.11.1.), and it was evident that both spontaneous and photically induced 3 c.p.s. spike and wave activity was responsive to sodium valproate treatment. As Daly and Bickford (1951) regarded

this activity as of diencephalic origin, and noted the rarity of photosensitivity in focal cortical epilepsy, the evidence begins to point to photosensitivity as a sub-cortical dysfunction.

However, there has been some argument as to the exclusiveness of 3 c.p.s. spike and wave being entirely of sub-cortical origin. Depth EEG recordings in man showed that generalised spike and wave varied from patient to patient so that there was no consistent focal source of a generalised spike and wave pattern either cortically or sub-cortically (Laws, Niedermeyer and Walker 1970). Electric-shock stimulation of thalamic nuclei in monkeys indicated that the cerebral cortex might be influential in the genesis of spike and wave complexes (Steriade 1974). He postulated that initial specific thalamic stimulation drove the discharge along interneuronal groups and consequently self-sustained activity was generated within pools of cortical interconnected neurons. Impairment of consciousness might result from synchrony between different focal cortical generators with subsequent recruitment of long-axoned neurons and spread of activity to cortical brain regions.

The amplitude of the EEG signal is dependent upon synchrony and the area of which activity occurs (Cooper et al. 1965). While both generalised bilateral atypical 3 - 4 c.p.s. spike and wave and polyspike and wave of varying frequency were equally as frequent in the spontaneous EEG, the latter type of discharge was nearly twice as common during IPS. This pattern of activity therefore suggests global interference of discharge from more than one generator, probably with differences in oscillation frequency due to variations in refractory period,

number of neuronal groups in a chain and possibly metabolic differences.

Latterly, the visual cortex has become strongly linked with photosensitive mechanisms. In man, the occipital cortex is suggested as having an innate epileptogenic potential (Naquet et al. 1960; Ludwig and Marsan 1975). In 'occipital-lobe epilepsy' spontaneous and photically evoked abnormality are mainly confined to the occiput, and the characteristic spike discharge is thought to be an abnormal augmentation of the VEP (Naquet et al. 1960). However, this differs from classical photosensitive epilepsy for, whereas focal repetitive spiking was the most common EEG paroxysm in the former condition, in the present study only 17% of photosensitive patients had spontaneous occipital spikes and up to 56% photically evoked occipital spikes compared to all patients showing bilaterally generalised PCRs.

Bickford et al. (1953) proposed three possible pathways for the pathophysiology of photosensitive epilepsy. Two of these involved the visual striate cortex. One pathway consisted of the transcortical spread of abnormality initiated in the visual cortex and another was the stimulation of the diffuse thalamic system by efferent activity from the occiput which, in turn, triggered spike and wave. However, they failed to detect any extension of a convulsive process in their patients, with subsequent involvement of the remaining cortex, and thought these pathways unlikely. In relation to this, others have noticed the mutual exclusiveness of photic activation and photic driving. Daly and Bickford (1951) observed that below threshold level normal photic driving occurred, and above it paroxysms appeared abruptly without

enhancement of the driving response. Brazier (1953) similarly believed that the cortex was not a 'way station in the pathology of photic activation'. She found that while photosensitives reacted to critical flash frequencies, they were generally impervious to rhythmical EEG activity at that frequency, elicited as a secondary haromic response by half the flash rate. It was concluded that the trigger mechanism did not therefore lie on the specific visual pathway to the cortex but in the sub-cortical system leading through collaterals in the brain stem.

In the present study, sodium valproate appeared to exert no significant effect on photic driving as before, during and after treatment no significant differences were observed between patients and matched normal controls as regards the range and upper limit of the driving response. Also, it was noted that although the PCR and photic driving were mutually exclusive, a brief run of driving might occur before a PCR but with no particular buildup in amplitude. However, at all stages of treatment, even with significant improvement in photosensitivity, the lower limit of photic driving did occur at a significantly lower flash rate in photosensitives; which in part may have been due to the increased amplitude of the cortical driving response in these patients allowing easy detection during visual analysis of the EEG. It was also evident that before PCR onset, augmentation of the driving response did occur when it was combined with occipital spikes at the same rate. In general, approximately 50% of photosensitives have PCRs triggered by occipital spikes.

Panayiotopoulos et al. (1972) proposed that the non-specific thalamo-cortical system might be implicated in the

genesis of occipital spikes and drew comparisons between the similarity of this localised abnormality with the recruiting response (RR). The response was initially found by stimulation of the rostral and mesial points of the reticular system and anterior fornix, producing foremost responses in the parieto-occipital cortex. Projection to posterior cerebral regions was better during lateral thalamic-reticular stimulation (Jasper 1949). The optimal stimulation frequency was 6 - 12/sec. The RR was characterised by a successively increasing cortical surface negative wave reaching a maximum after 2 - 5 stimuli; with continued repetitive stimulation the RR waxed and waned in amplitude; it had long latencies in comparison to the latencies of specific responses, suggesting passage through polysynaptic connections; the waves of the RR were synchronised to the frequency of the stimulus (Jasper 1949; Verzeano, Lindsley and Magoun 1952; Himwich 1961). However, Verzeano et al. (1952) found that stimulation of the diffuse projection nuclei promptly conducted the discharge both to the thalamic-reticular system and the cortex and that subsequent activity developed independently in both areas. In each structure the RR appeared to arise from oscillation of impulses along closed chains of neurons, and the fact that the RR at the thalamus and cortex were alike was considered to be due to the similarity between the closed neuronal chains. They suggested that the delayed latency of the RR was due to the reverberation of activity in cortical elements for several milliseconds until a sufficient number discharged and generated the major negative wave of the response. The initial brief deflection was not considered as recruiting or affected by cortical excitability, and therefore represented incoming activity from the thalamus. All phases of the RR after this

brief response appeared to be of cortical origin.

It is interesting that in the present study the only effect sodium valproate had on occipital spikes was the disappearance of the single or brief spike precipitator when photosensitivity was abolished. This might be compared to the initial deflection of the RR from a thalamic-reticular site. However, persistent and rhythmical occipital spikes at the same rate as the flash remained even after disappearance of the PCR. If occipital spikes are comparable to the RR, it appears that sodium valproate may be preventing the spread of stimulation. However, the question still remains of how and where the initial incoming activity from the thalamus is originated?

Collaterals are believed to pass from the optic tract to non-specific thalamic- reticular nuclei (Jasper 1949; Moruzzi 1952). Several authors have implicated the lateral geniculate nuclei in photosensitivity. Bickford et al. (1953) proposed a third pathway; that due to the simultaneous occurrence of photically induced discharges in all cortical areas, activation might arise from the lateral geniculate to the diffuse thalamo-cortical system. Still believing red light to be more provocative in photosensitivity, Marshall et al. (1953) suggested that integration of red carrying elements at the geniculate level was involved. Hishikawa et al. (1967) finding increased sensitivity during REM sleep in comparison to other sleep stages postulated, on the basis of animal studies, that synaptic transmission was facilitated at the lateral geniculate body which in turn increased reticulo-cortical responsiveness in REM sleep and the waking state. However, Rodin et al. (1955) stated that a change in the lateral geniculate during sleep in fact increased the

threshold level at this point in the optic tract. Similarly, Meier-Ewert et al. (1967) and Broughton et al. (1969) found a diminished photoconvulsive tendency during REM sleep.

Hishikawa et al. (1967) considered the occipital spike to be unusually augmented components of the VEP. In patients where additional occipital abnormalities were found, they suggested that this augmentation was at the cortex and, in the absence of occipital abnormality, at the lateral geniculate body. The lateral geniculate contains mainly concentric receptive fields in the cat and monkey which are arranged so that sensitivity is enhanced to spots of light. The optimal size of the spot giving maximal sensitivity corresponds to the size of the cell's receptive field centre with a modal range of 7.5'- 30' of arc (Hubel and Wiesel 1960; 1962). In the present study, flashed-on grid pattern was somewhat more effective than the checkerboard pattern at low flash rates, even though individual squares in both stimuli subtended a 12' visual angle, despite any increase in light intensity of the checkered stimulus. Besides providing the visual cortex with more contrast borders, angles and fine bars to stimulate maximally the complex and hypercomplex cells (Hubel and Wiesel 1968), the grid pattern produced double the amount of small spots of light, compared to the checkerboard, which impinged on to the geniculate body.

It is questionable, however, even if collaterals subserve a relay from the lateral geniculate to hypersensitive thalamic areas, whether the occipital spike at the cortex is the direct result of afferent impulses in the specific pathway. The long latencies of the occipital spike have been proposed as not in favour of transmission in the optic tract

(Creutzfeldt and Kuhnt 1967; Panayiotopoulos et al. 1972). If the geniculo- cortical volley were increased, the spikes would be expected to occur earlier.

There has been much controversy over the modality specific and non-specific nature of VEP components, in particular those occurring after a delay of 120 msecs. from stimulus onset. Originally Cigánek (1961) suggested that the first three waves (0 - 90 msec.) represented a primary response following a specific pathway through the geniculate bodies, and that later components (90 - 240 msec.) were a non-specific secondary response arising in diffuse polysensory thalamic pathways due to the long latencies, suppression by increased flash rate and marked alteration by both stimulus and subjective variables. The real visual response also came to be regarded as the initial positive deflection (20 - 25 msec.) observed by Cobb and Dawson (1960) (Bergamini and Bergamasco 1967). However, Spehlman (1965) stated that the late wave (180 - 375 msec.) was a truly specific component due to its dependency on type of visual input and topographical distribution over the cortex. The entire VEP was regarded by Gastaut and Régis (1964) as being strictly connected with vision, although there was no direct dependence on the optic radiation. They proposed that the positive wave at 100-120 msec. was related to photopic mechanisms of the macular. It was considered that the late negative wave at the occiput (120 - 160 msec.) was in common with the vertex sharp wave (Creutzfeldt and Kuhnt 1967). However, Lehtonen (1973) observed enhanced amplitude of the occipital wave and related it to the findings of others; that a negative-positive sequence in the 120-260 msec. range is more sensitive to field size of a contoured stimulus (Spehlman 1965; Rietveld et al.

1965; Harter and White 1970; Kooi et al. 1972). The vertex wave was, however, attenuated and the author proposed that the occipital late wave reflected the function of a modality specific cortical area and that of the vertex a non-specific area.

Creutzfeldt and Kuhnt (1967) postulated that the VEP consisted of compound inhibitory (IPSP) and excitatory (EPSP) post-synaptic potentials of cortical cells as well as afferent and efferent fibre activity. The positive waves were considered as part of a large post-synaptic inhibition of cortical cells which were not elicited directly by thalamo-cortical afferents but through intra-cortical recurrent collaterals. Cigánek's first three waves were regarded as one large negative potential and this, together with the late negative wave, were considered as non-specific excitation superimposed on the long lasting IPSP. However, as flash rates increased above 5 - 10 f.p.s., IPSPs diminished and disappeared by 10 - 15 f.p.s. (Kuhnt and Creutzfeldt 1971). This reduction was also accompanied by an unmasking of EPSPs. The amplitude of the EPSP was also reduced at stimulus frequencies above 10 - 12 f.p.s. as a result of decreased firing in sensory afferent fibres. This may partly account for the reduction in the photic driving response described at higher frequencies by Kinney et al. (1973). Although the excitation of cortical cells per stimulation might be less at high flash rates than during a single stimulus, the overall afferent activity was highest at 10 - 15 f.p.s. It is suggested, therefore, that above 5 - 10 f.p.s., these factors are related to increased epileptic activity during IPS (Kuhnt and Creutzfeldt 1971).

From the studies on flashed-pattern IPS and the VEP, it was obvious that at low flash rates the VEP was particularly enhanced in photosensitives compared to controls during optimal stimulation of the macular. The macular has greater cortical representation than other retinal areas and is situated nearest the outermost surface of the brain. Although it has been suggested that this proximity to the scalp accounts for the observed response (Van Balen et al. 1966), Chatrian et al. (1970a) found that generalised spike and wave over all cortical areas was particularly evoked with patterned stimulation of the macula in pattern-sensitive epileptics. In agreement with other VEP studies previously discussed, the amplitude of the overall P2 component (N2 - P2 - N3 sequence) was influenced by pattern and visual field size. This corroborates the findings of Gastaut et al. (1966), that P2 is related to photopic function of the macular. Although it was evident that both early and late components were all connected to vision, whether or not N2 and N3 originated from 'non-specific' but topographically directed sites in the thalamic-reticular system, there certainly appears to be facilitation of this activity at the visual cortex in photosensitives. The increased amplitude at 8 f.p.s., when EPSPs are gradually developing, further supports the idea of a latent hyper-excitability within this striate cortex. As previously mentioned, only a few patients exhibited spontaneous abnormality but photic stimulation elicited this hyperexcitability in the form of an enhanced VEP and also, in half the patients, as a definite spike abnormality. It was also noted that when sodium valproate acted upon the generalised PCR, it often became degraded; maximal amplitude remaining in the occipital regions with poor frontal extension.

The occipital spike was found to be directly related to macular stimulation and the major inhibitory component P2, which is in agreement with Dimitrakoudi et al. (1973). It was possible for the occipital spike to develop from the triphasic P2ab component, but sometimes it spontaneously appeared, usually at the base or descending arm of P2. It was also possible for patients who did not show occipital spikes to possess a small P2ab component from 1 - 9 f.p.s. or at very low flash rates which later disappeared. Similarly, the P2ab component was not unusual in control subjects at the faster frequencies , but at 1 f.p.s. this component was significantly more common in photosensitives. In fact 16% of patients had occipital spikes at 1 f.p.s. As mentioned, when flash rate increases, IPSPs diminish and EPSPs increase. It may therefore be that this transition is expressed sometimes in the appearance of a small excitatory P2ab potential, but that in half the photosensitives the increase in cortical excitability causes a failure in the inhibitory processes which results in an occipital spike, as suggested by Jeavons and Harding (1975). The P2ab component and occipital spike may therefore represent varying degrees in lack of inhibition which, in some photosensitives is present even at 1 f.p.s.. In a few patients it was definitely the N2 component which became enhanced and whether or not this wave originated from thalamic systems it was probably augmented at the cortex.

It was notable that although sodium valproate reduced the amplitude of the N2 - P2 - N3 sequence to some extent; even after total abolition of the PCR the overall P2 amplitude remained significantly greater than that of controls at 1 f.p.s. and there was similar indication at 7 and 9 f.p.s..

Also, throughout the study spontaneous and photically evoked occipital abnormalities were the most resistant to treatment. It is possible, therefore, that sodium valproate was acting on the thalamo-reticular connections to and from the cortex, suppressing the spread of generalised spike and wave and diminishing superimposed excitation within the VEP. The lack of inhibition within recurrent intra-cortical neurons, however, was unaffected and still gave rise to persistent occipital spikes. In particular, it was found that when all trace of generalised abnormality had been removed, the rhythmical occipital spikes ceased around 11 - 13 f.p.s., which coincides with the disappearance of cortical IPSPs, described by Kuhnt and Creutzfeldt (1971). With reference to the studies of Verzeano et al. (1952) and Steriade (1974), it is possible that up to these flash frequencies the reverberating circuits within the cortex could still elicit occipital spikes. However, if within the sodium valproate treated patient the 'non-specific' nuclei within the thalamic-reticular system now possessed a greatly increased seizure threshold, generalised spike and wave could no longer be triggered by the occipital spike and propagated to other cortical areas.

Lloyd-Smith and Henderson (1951) suggested that in photosensitive epilepsy cortical discharge in visual areas is increased and transmitted at an early stage to the motor cortex, between which existed a close functional relationship. Bablouzian et al. (1969) observed a spread of certain VEP components to the central region indicating an irradiating role from visual to motor cortex in the genesis of photic-induced seizures. However, they did suggest that this might be primarily occurring at sub-cortical levels. There does

appear to be a close relationship between occipital and central cortical areas. Siegel, Coleman and Riesen (1973) reported that in visually deprived kittens reared in diffuse light, a lack of visuo-motor co-ordination developed. Certainly IPS is evocative in eliciting myoclonic jerks with accompanying polyspike discharge, even in patients with no clinical history of myoclonic fits (Jeavons 1966). In the present study, polyspike PCRs occurred in 18.5% of patients. However, although occipital spikes were seen to precipitate polyspike and wave and atypical 3-4 c.p.s. spike and wave, typical 3 c.p.s. spike and wave and polyspike PCRs were not precipitated by occipital spikes. As previously mentioned, the first pathway proposed by Bickford et al. (1953) in the pathophysiology of photosensitive epilepsy was the transcortical passage of spike and wave from the visual striate cortex. However, if photosensitivity did involve the transcortical passage of paroxysmal discharge from the occipital area, then sodium valproate would not have affected the PCR, due to the fact that cortical occipital spikes were seen to remain during treatment.

As previously mentioned, the thalamic- reticular system possesses no 'all or nothing law', unlike the cortex, but excitation is by degrees (Moruzzi and Magoun 1949; Luria 1973). This probably explains sodium valproate's differential affects upon the spontaneous and photically activated EEG. The threshold level increased to such an extent that generalised spontaneous abnormalities disappeared. However, further increase gradually occurred until the threshold levels were sufficiently high to block massive excitation during IPS. Such a buildup within centrencephalic systems is evident from the gradual effects of sodium valproate on the PCR itself;

delayed onset, diminished amplitude and reduced persistency (particularly in the form of isolated mid-, off- and on-responses). Also it was the upper limit of photosensitivity, found to be dependent on flicker frequency per se and not pattern stimulation, that responded first to treatment. The lower limit was particularly influenced by optimal stimulation of the visual cortex and, as occipital spikes often occurred at flash rates below the PCR threshold, it appears that cortical facilitation provided additional stimulation of thalamic-reticular sites and aggravated the lower limit of photosensitivity. This seems probable as relapse during treatment was seen in three patients, all with occipital spikes, and after withdrawal of sodium valproate a return of photosensitivity promptly occurred at the low flash rates, whereas the upper limit continued to show a continuing but gradually decreasing effect of the drug.

Period analysis of the background EEG activity in posterior derivations indicated that during sodium valproate treatment theta activity in the resting EEG was associated with a marked improvement in photosensitivity, although it failed to reach statistical significance. The activity within cortical sensory areas has been shown in animals to depend to some extent upon the functional state of certain parts of the limbic system, and it is possible that limbic facilitation may involve the non-specific thalamic systems (Sierra and Fuster 1968). Sensory input on reaching the hippocampus is characterised by universal theta activity (Magoun 1958). Scollo- Lavizzari and Hess (1967) attributed decreased sensitivity during REM sleep to inhibition of the thalamo- cortical system. REM was characterised by its

cortical LVFA and hippocampal theta activity. Schmidt and Wilder Wilder (1968) described atypical absence seizures as originating in the amygdalo-hippocampal circuits and projecting to the striate system from the hippocampal gyrus. Although it is a tentative suggestion, the increased theta activity seen in successfully treated photosensitive epileptics may indicate increased inhibition within the Papez circuit which, as previously mentioned, is closely linked with the thalamic-reticular system.

In relation to this proposal, signals ascending in less specific routes through the ARAS are conducted from the septum into the hippocampus through centripetal fibres of the fornix. As mentioned previously, the surgical section of the fornix prevents the spread of spike and wave to parieto-occipital areas (Magoun 1958). This author also discusses the link between the hippocampus and the processing of memory and learning. Epileptic patients may experience behavioural and intellectual difficulties, although the reasons why are highly controversial (Schmidt and Wilder 1968). The general opinion from clinical studies with sodium valproate is that epileptic patients become more alert, self-confident, competent and their powers of concentration improve (see Section 4.12.2. In the present study, many photosensitive patients experienced a feeling of wellbeing during treatment. The contigent negative variation(CNV) and reaction time (RT) have been standardly used as measures of attention, distraction or arousal (Tecce, Savignano-Bowman and Meinbresse 1976). There is, in fact, experimental evidence that sodium valproate does decrease CNV amplitude and shortens RT (Harding and Pullen - personal communication). Improvement in behaviour generally

accompanies suppression of epileptic seizures (Hassan et al. 1975) and mental stimulation can occur with sodium valproate alone or in the absence of any change in previous drug dosages (Mairlot 1970; Jeavons and Clark 1974; Grant and Barot 1975; Timpany 1975). It is possible, therefore, that sodium valproate may also act upon the higher limbic- cortico connections within the Papez circuit.

The precise site of this drug's action within sub-cortical systems may be dependent on which transmitter substances are affected. However, this is still a matter for speculation. Standard anticonvulsants have been shown to have no appreciable influence over photosensitivity (see Section 5.1.), and some clue of how sodium valproate differs in this aspect may be derived from the mode of action of other drugs, e.g. barbiturates are thought to exert their anticonvulsant action on acetylcholine neural synapses within the CNS, and block or slow down the sodium-potassium pump resulting in a dampening of both excitatory and inhibitory potentials; trimethiadone (like ethosuximide) was previously the drug of choice for absence seizure and will remove spontaneous 3 c.p.s. spike and wave by exerting its anticonvulsant action on the lateral thalamus; benzodiazepines suppress electrically induced afterdischarge in the limbic system, including the septal region, amygdala and hippocampus. These drugs block strychnine seizures (Schmidt and Wilder 1968) whereas sodium valproate does not (Lebreton et al. 1964b; Olive et al. 1969). However, diazepam (iv) does have a temporary effect on photo-sensitivity (Poiré et al. 1967; Ebe et al. 1969) and clona-zepam has improved the EEG and clinical signs of photo-sensitive epilepsy (Rail 1973; Hooshmand and Oliver 1975;

Ames and Enderstein 1976), although the outcome has been variable with adverse side-effects.

The major inhibitory transmitter substance, GABA, has been associated with the anticonvulsant action of sodium valproate, although there is no straightforward explanation of this being mediated solely by elevation of brain GABA through degradative enzyme inhibition (see Section 4.7.). Also, insignificant changes in GABA levels associated with definite anticonvulsant action of sodium valproate indicate the involvement of other factors (Pinder et al. 1977). However, it is interesting that in the human brain GABA concentration is correlated with its synthesising and not its degradative enzyme, highest levels occurring in the globus pallidus, dendate nucleus and substantia nigra (Fahn and Côté 1968). In monkey cortex these authors found a similar pattern of distribution; lowest levels occurred in the lateral and anterior thalamus and frontal, motor and occipital cortex.

In conclusion, therefore, the action of sodium valproate on the characteristic responses of photosensitive epilepsy, indicates that a low seizure threshold definitely exists in the 'non-specific' thalamic- reticular connections with the cortex and therefore supports the proposals of Doose et al. (1969b) and Panayiotopoulos et al. (1972). However, in the majority of photosensitives there also appears to be facilitation of activity in the visual cortex at low flash rates, which in approximately 50% of patients may lead to a failure of inhibitory mechanisms within the striate area and, in turn, trigger the photoconvulsive response.

9.3. Prognosis and Prophylaxis.

A PCR does not necessarily indicate a clinical diagnosis of photosensitive epilepsy but there is an 80% chance that an epileptic condition does exist, which is increased if the patient has an epileptic relative (Jeavons and Harding 1975). Over a period of 12 years, 167 photosensitive patients were monitored at approximately yearly intervals. Although the age range varied between 5 - 40 years, the mean age was 13 years 5 months, which corresponds with the findings of age and heightened photic activation (Doose et al. 1969a, b; Jeavons and Harding 1975). However, although a wide variation was seen between the degree of improvement and deterioration in the lower limit of photosensitivity, overall no significant trend was observed and, after 12 years from onset, photosensitivity was still exhibited by some patients.

Treatment with sodium valproate showed that significantly more photosensitive epileptics could be cured by taking this drug, and within a significantly shorter time, than would normally occur. Although the action of sodium valproate was not influenced by clinical history, the probability of purely flicker- sensitive patients being cured was far greater with sodium valproate therapy. As long as patients continued with the treatment, the beneficial effects on the basic EEG, photosensitivity and clinical events were highly stable. However, slight relapse in photosensitivity did occur in a few patients with persistent occipital spikes.

Doose and Gerken (1973) recommended the use of sodium valproate in the prophylaxis of symptom-free siblings of photosensitive epileptics showing PCRs during photic

stimulation. In the present study, one female sibling (aged 7 years 4 months) was photosensitive during IPS and had an abnormal basic EEG. On a very low dosage of 600 mg/day of sodium valproate alone, the EEG became normal and photosensitivity was abolished within two months. Drug withdrawal was accompanied by a return of photosensitivity. Due to the minimal side-effects of sodium valproate, it might therefore be used prophylactically at the discretion of the medical practitioner.

In conclusion, it is evident that sodium valproate must be the first drug of choice for photosensitive epilepsy. EEG normalisation was seen in 61%; full control of photosensitivity in 54%, and significant improvement in a further 24% of patients. As this was an ongoing study, it is highly probable that some of this 24% have now also achieved full control. The site of sodium valproate's anticonvulsant action appears to be in the regulation of thalamo-cortical transmission.

9.4. Future Research.

A complete understanding of the physio-chemical mechanisms involved in photosensitive epilepsy requires further study into the effects of this drug on both inhibitory and excitatory transmitter substances within defined subcortical and cortical areas of the brain, viz. GABA and the monoamines. Scientific study into the behavioural effects of the drug in photosensitives, in combination with the monitoring of sensitivity ranges, besides strengthening the suitability of sodium valproate for children in particular, may provide further evidence for the drug's mode of action. Similarly, controlled sleep studies in normals and photosensitive epileptic volunteers before, during and after withdrawal of sodium valproate could illustrate the drug's effect on spontaneous and photically induced activity during the sleep-wakefulness cycle.

More conclusive information on spontaneous background EEG effects may also be revealed by reanalysis of the EEG data stored on magnetic tape, used in the present study, by other computerised methods sensitive to amplitude changes and frequency components of a particular waveform.

A better indication of the effects of sodium valproate withdrawal on photosensitivity could be found through more frequent follow-up investigations, viz. weekly repeats particularly within the first month.

The exact influence of pattern on the photosensitive VEP and EEG activation requires investigation using techniques of pattern-motion and pattern-reversal. As with the flashed-on pattern, stimuli could be devised for differential stimulation of retinal locations at slow and fast alternation rates that correspond to the critical activation frequencies during IPS.

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Epilim and photosensitivity

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Since 1964 we have been studying patients with photosensitive epilepsy, and up to 1973 it was our practice not to use anticonvulsants in those patients whose fits were induced only by flickering light and whose basic EEG showed no spontaneous spike-and-wave abnormality.

There is little evidence that anticonvulsants affect the photoconvulsive response (PCR), the only exception being ethosuximide in those patients in whom intermittent photic stimulation (IPS) induces a 3 cycle per second spike-and-wave absence. The therapy we recommended was avoidance of the stimulus; thus patients were advised to view television only in a well-lit room from a distance of more than 2 metres, and never to approach the set to switch or adjust it. If the patients had to switch the set or were suddenly faced with flickering light in a discotheque, they were advised to cover one eye. The hazard of flickering sunlight reflected off wet surfaces was reduced by wearing polarising spectacles.

Doose and Gerken[1] suggested the possibility of using dipropylacetate in the prophylaxis of those symptom-free siblings of photosensitive patients who showed a PCR on photic stimulation. Between October 1973 and August 1975 we have studied the effect of Epilim on the photoconvulsive response, the visual evoked potential and the background resting EEG of various patients with photosensitive epilepsy. During this period patients were studied initially to ascertain their degree of photosensitivity, and subsequently were treated with various doses of Epilim. Since this is an on-going study, patients are at various daily dose levels, and not all patients have yet reached the maximal daily level of 1,400 mg.

The study involved determining the reliability of the photosensitivity range and of the scoring system used to assess the spontaneous background activity of the EEG, and a study of the visual evoked potential. Each patient usually had two EEG records prior to receiving the drug. The dosages of Epilim were 400, 600, 800, 1,000 and 1,200 mg daily, and at each dose level both the spontaneous EEG and the photosensitivity range were compared to those in the second of the pre-drug records.

CLINICAL GROUPS

Thirty-seven patients have so far been studied. Twenty-two had fits only when exposed to flickering light encountered in everyday life; 10 had spontaneous fits as well as fits induced by flicker; and 5 had epilepsy without any clinical evidence of precipitation by flickering light. All patients showed photoconvulsive responses on intermittent photic stimulation. The commonest type of fit induced by flicker was a tonic-clonic seizure, but a number of patients had several different types of fit (Table I).

Table I Types of fit induced by flickering light

Tonic-clonic	16
Absences	1
Myoclonic jerks	4
Focal motor	1
Mixed fits	15
Total	37

BASIC EEG RECORD

The EEGs were classified as abnormal, non-specifically abnormal, and normal. The record was rated abnormal only if there were bilateral or local discharges of spike-and-wave or spikes. Non-specific abnormality refers to slow waves or doubtful non-localized sharp waves. The percentages of abnormal records at various stages of the investigation are shown in Figure 1. Because EEGs were rarely taken at dose levels of 400 and 600 mg daily, the results at these points are omitted. Abnormality commonly disappeared from the basic EEG when the dose of Epilim reached 1,000 mg daily.

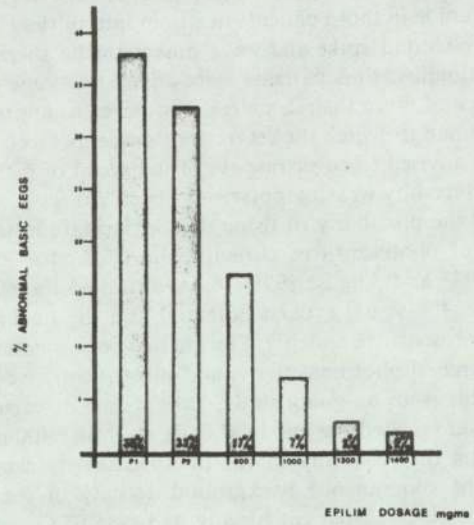

Fig. 1. – Indicates the percentage of basic EEGs which showed spontaneous abnormality in the two pre-drug recordings (P1 and P2) and at Epilim dosage levels of 800, 1,000, 1,200 and 1,400 mg daily.

SENSITIVITY LIMITS OF PHOTOCONVULSIVE RESPONSES

The sensitivity range is defined as those flash rates which consistently evoke spike-and-wave or polyspike-and-wave photoconvulsive responses. The lower limit of the sensitivity range is usually more easily defined than the upper, owing to the tendency of photostimulators to produce subharmonic components when set at faster flash rates. The sensitivity range is obtained by subtracting the lower limit from the upper, thus indicating the number of flash rates to which the patient is sensitive.

In a previous study of 36 patients[2] we investigated the long-term test-retest reliability of the upper and lower sensitivity limits; the EEGs were repeated within a 3 month period, and the patients were not receiving drugs. The age range of the patients was 7 to 30 years. The reliability of the lower limit was greater than that of the upper limit; the standard deviation of the upper limit was 10.4 and that of the lower limit 5.9 flashes per second (f/sec).

The reliability of sensitivity limits was tested for 24 of the 37 patients in the Epilim trial by comparing the paired records taken before the administration of the drug, and the findings were essentially similar to those in the larger sample of 36 patients. In the subsequent trial the sensitivity limits obtained at the various drug levels were always compared to those in the second of the pre-drug records.

It should be noted that the intensity of the photo-stimulator (Grass PS. 22) was always constant, and was equivalent to 1,363 nits for all patients at doses of 800, 1,000 and 1,200 mg daily.

Twenty patients were studied at a dose of 800 mg. The results are shown in Fig. 2, in which improvement in the upper limit is shown by a shift to the left and improvement in the lower limit by a shift to the right. In 3 patients there was no longer any abnormality on photic stimulation. Eight patients showed improvement greater than the standard deviation of the upper limit and 5 showed a similar improvement in the lower limit.

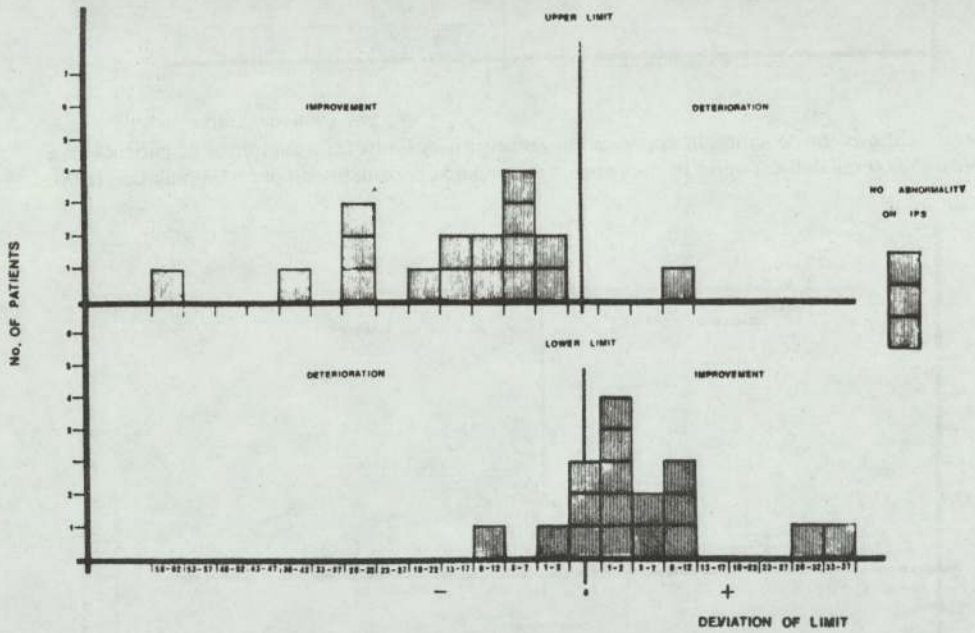

Figure 2. – Shows the deviation in upper and lower sensitivity limit at an Epilim dosage of 800 mg daily, in a sample of 20 patients. Each block indicates 1 patient and it can be seen that 3 patients showed no abnormality on photic stimulation (IPS) and that there was a reduction in the upper sensitivity limit and an increase in the lower sensitivity limit in most patients.

The results in 22 patients on a dose of 1,000 mg daily are shown in Fig. 3. All abnormality on photic stimulation had disappeared in 12 patients, 4 showed improvement in the lower limit, and there were 6 with similar improvement in the upper limit. One patient who had shown a wide range (7–68 f/sec) in the first pre-drug record showed a narrow range (9–25 f/sec) in the second pre-drug record, with which the comparisons have been made.

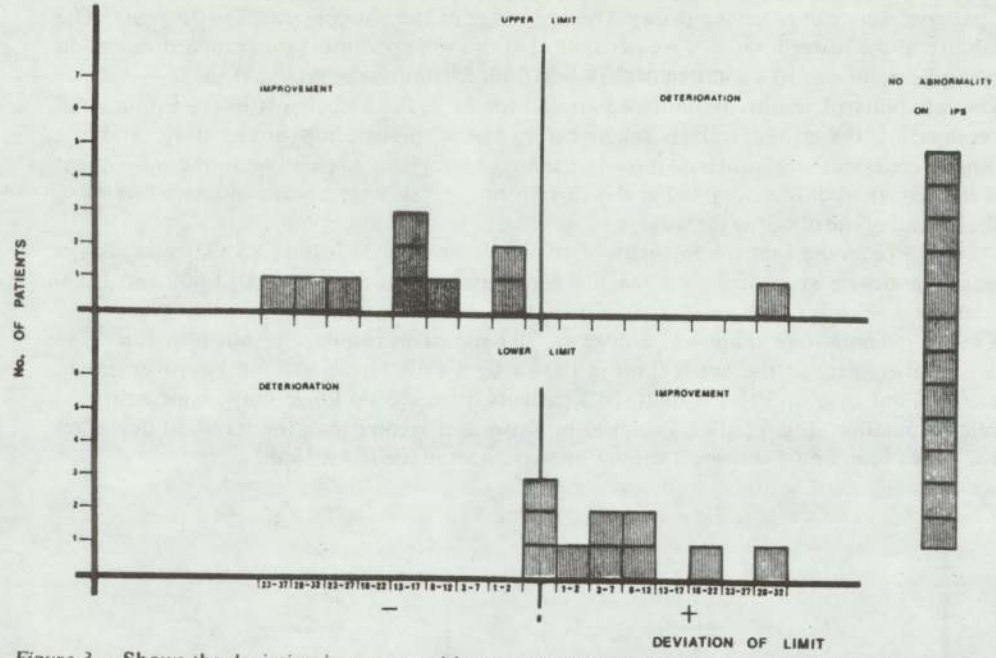

Figure 3. – Shows the deviation in upper and lower sensitivity limits for a sample of 22 patients on a dosage of 1,000 mg daily. Twelve of the patients showed no abnormality on photic stimulation (IPS).

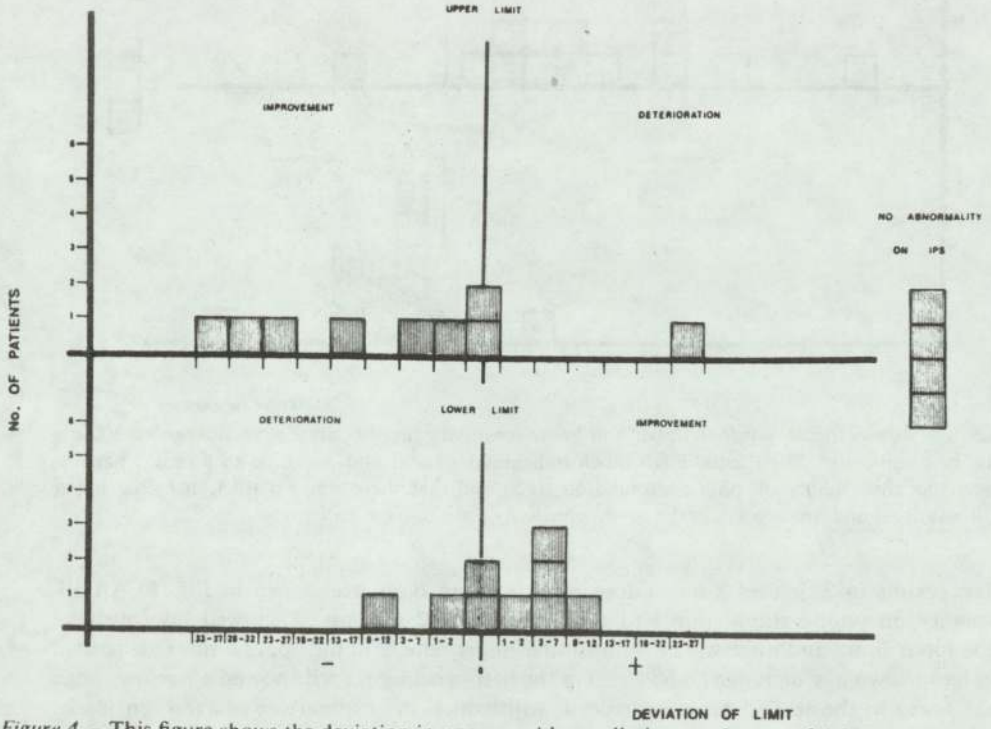

Figure 4. – This figure shows the deviation in upper and lower limit at a dosage of 1,200 mg daily in a sample of 13 patients. Four patients showed no abnormality on photic stimulation (IPS).

At 1,000 mg (Fig. 3) the range was 40–55 f/sec, i.e. narrow and high. On a dose of 1,200 mg (Fig. 4) the range was 9–52, similar to that seen in the first pre-drug EEG.

Thirteen patients received a daily dose of 1,200 mg of Epilim, and 4 showed no EEG abnormality. One showed improvement in the lower limit and 4 in the upper limit.

Thus photoconvulsive responses are no longer present in 18 patients, who can therefore be regarded as having shown 100% improvement with Epilim.

OCCIPITAL SPIKES

It was apparent from our previous study[2] that photic stimulation evoked occipital spikes in most patients who showed a PCR. However, a number of patients showed no obvious occipital spike on visual inspection of the EEG, but did show such spikes in their visual evoked potential (VEP). Twelve patients who showed occipital spikes and PCRs in the pre-drug EEG were examined at daily Epilim dose levels of 1,000 and 1,200 mg. At 1,000 mg all 12 still showed occipital spikes and 11 continued to show a PCR. At 1,200 mg all 12 still showed occipital spikes but in 5 the PCR had disappeared.

Epilim was found to have the greatest effect on abnormalities in the basic EEG, to be effective on photoconvulsive responses at a higher dose, and to have little effect on occipital spikes.

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DISCUSSION

Bower: You have told us about the response in the EEG. Can you tell us anything about the clinical correlates of this?

Jeavons: There really are no clinical criteria in these patients, because they only get fits if they sit too close to the television, and we have advised them not to do this. But if we can abolish their photosensitivity altogether they may become eligible for a driving licence, which is very important.

Legg: You said that other drugs did not have any effect on the photo-convulsive response. Have you, or nas anyone else, undertaken trials of traditional anticonvulsants using the type of assessment you have been describing for Epilim?

Jeavons: No.

Parsonage: Three of your patients showed no response at all; can you give any reason for this difference?

Jeavons: No, but the trial is still going on and dosages may yet have to be increased.

Meinardi: What about the drug effects on Papio papio? Surely effects have been described on their photo-convulsive responses?

Jeavons: I think this is probably a different matter from the human photo-convulsive response, as it seems undoubtedly to involve eye-muscle movements in the animal.

Espir: What is the natural history of photosensitivity? Do children grow out of it, and do we in fact need to treat it?

Jeavons: We can only suspect this at the moment. We are undertaking a long-term follow-up study, but it is going to take about 15 years to find out.

Wigglesworth: Why do you instruct them to cover one eye?

Jeavons: It halves the number of stimuli which reach the retina and the cortex, and therefore reduces the chances of evoking a fit.

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34

Therapy and prophylaxis in photosensitive epilepsy

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Since 1964 we have studied nearly 500 patients with photosensitivity, all of whom show a photoconvulsive response (PCR), most commonly spike and wave, when exposed to intermittent photic stimulation (IPS). Abnormality is usually not present with monocular stimulation or when the patient looks to the side instead of directly into the lamp of the photostimulator. About half the patients have a normal basic EEG and these patients do not usually need to take anti-epileptic drugs provided they take certain simple precautions when viewing television or when exposed to other forms of flickering light encountered in everyday life (Jeavons and Harding 1975).

We advise that the television is viewed from a distance greater than two metres, in a well lit room, with an illuminated table lamp on top of the set. The patient should never switch or adjust the set, but if it is essential to approach the screen, they place the palm of their hand firmly over one eye. A similar action should be adopted in discotheques or with Pop groups if flashing lights are used. Polarising spectacles are worn in sunny weather to avoid the hazard of reflected sunlight flicker.

In one family with 11 siblings, two boys and a girl had had a fit when watching television and all had normal basic EEGs but PCR on photic stimulation. Three other boys had no definite abnormality on IPS, and the mother had a mild abnormality. Of five other sisters, three showed spike and wave on IPS although none had had a fit. Precautions when viewing TV are now taken by these clinically „normal" siblings.

There is little evidence that anti-epileptic drugs have any effect on spike and wave discharges evoked by IPS, apart from the rare patients (7% in our series) in whom IPS induces a typical absence with 3 c sec spike and wave lasting 10—20 seconds. These patients

may respond to ethosuximide, though this drug has little or no effect on other types of photosensitive epilepsy.

We have given sodium valproate to 35 patients with photosensitive epilepsy, in doses from 600 to 1400 mgm daily. The responses to IPS are tested before the trial and then at each dose level, the dose being increased until no abnormality is evoked by IPS. The following factors are standarized for each test: type of photostimulator, environmental illumination, intensity and colour of light, transmission and diffusion, distance from light source, direction of gaze, rates of flash, duration of stimulus. The upper and lower sensitivity limits are defined for each patient, the sensitivity limit being the flash rate which consistently evokes spike and wave or polyspike and wave PCRs.

Percentage improvement can be based on the degree of change in the limits. Abnormal discharges disappear first from the basic EEG, often at a dose of 1000 mgm or less. At this daily dose of 1000 mgm, 12 of 22 patients no longer showed any abnormality on IPS. Although the investigation is not yet completed, the EEGs have become entirely normal in 20 of the 35 patients, and another 7 have improved by more than 80% (Fig. 34.1).

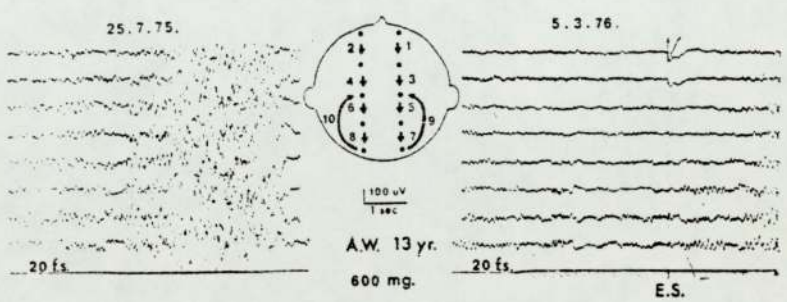

Fig. 34.1. Television epilepsy. Photic stimulation at 20 flashes per second evoked photoconvulsive response on 25.7.75. No abnormality evoked by same flash rate, even on eye closure (E.S.), after treatment with 600 mgm sodium valproate daily.

We have also treated 25 patients who have spontaneous fits as well as being photosensitive. Many had failed to respond to anti-epileptic therapy with a wide variety of drugs. Sodium valproate was added to their current medication and subsequently other drugs were withdrawn in 5 cases, whilst reduction in dose was made in others. Eight patients have eyelid myoclonia and absences and four are free from all fits and have a normal EEG, whilst the other four have improved more than 80%.

Eight of nine patients with myoclonic jerks and abnormality on IPS are now free from fits as are 10 of 11 with tonic-clonic seizures.

Table 34.1

Type of fit	*Degree of improvement*			
	Total	*100%*	*>80%*	*>50%*
Tonic-clonic	11	10	—	—
Myoclonic jerks	9	8	—	1
Eyelid myoclonia	8	4	4	—
Photosentisive only (TV)	35	20	7	4
Total	63	42	11	5

The overall results of sodium valproate in the therapy of photosensitive epilepsies are shown in Table I, complete control being obtained in 67%, and improvement greater than 80% being seen in an additional 17%. Sodium valproate seems to be the drug of choice for this type of epilepsy.

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