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AMBULATORY EEG MONITORING IN THE DIAGNOSIS AND
TREATMENT OF EPILEPSY AND RELATED DISORDERS

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Thesis submitted for the Degree of
Doctor of Philosophy

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July 1986

ASTON UNIVERSITY

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SUMMARY

Ambulatory EEG recording enables patients with epilepsy and related disorders to be monitored in an unrestricted environment for prolonged periods. Attacks can therefore be recorded and EEG changes at the time can aid diagnosis. The relevant literature is reviewed and a study made of 250 clinical investigations. A study was also made of the artefacts encountered during ambulatory recording. Three quarters of referrals were for distinguishing between epileptic and non-epileptic attacks. Over 60% of patients showed no abnormality during attacks. In comparison with the basic EEG the ambulatory EEG provided about ten times as much information. A preliminary follow-up study showed that results of ambulatory monitoring agreed with the final diagnosis in 8 of 12 patients studied. Of 10 patients referred for monitoring the occurrence of absence seizures, 8 showed abnormality during the basic EEG and 10 during the ambulatory EEG. Other patients were referred for sleep recording and to clarify the seizure type. An investigation into once daily (OD) versus twice daily (BD) administration of sodium valproate in patients with absence seizures showed that an OD regime was equally as effective as a BD regime. Circadian variations in spike and wave activity in patients on and off treatment were also examined. There was significant agreement between subjects on the time of occurrence of abnormality during sleep only. This pattern was not affected with treatment nor was there any difference in the daily pattern of occurrence of abnormality between the two regimes.

Overall findings suggested that ambulatory monitoring was a valuable tool in the diagnosis and treatment of epilepsy which with careful planning and patient selection could be used in any EEG department and would benefit a wide range of patients.

ambulatory; electroencephalogram; monitoring
epilepsy; non-epileptic attacks;
sodium valproate

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PHILIPSON

1968

CHAPTER 1

HISTORICAL BACKGROUND

1.1 EPILEPSY IN ANCIENT TIMES AND THE
MIDDLE AGES

At various times throughout history the term epilepsy has been synonymous with, evil omens, demoniacal possession, impiety and lunacy. At the same time it has been linked with personal greatness, communication with God and the gift of foresight. Remedies have ranged from prayer and fasting to the wearing of peony root.

Such contradictions illustrate how epilepsy, due to its various forms and unpredictable nature, has been greatly misunderstood and even today often remains so.

A detailed history of the "falling sickness" (the term used in medieval literature to describe epilepsy) is given by Temkin (1945) extending from the earliest clinical documentation of epilepsy in the Hippocratic writings of 400 B.C., to the work of Hughlings Jackson in the nineteenth century. Temkin views the history of epilepsy in the light of religious, philosophical and scientific beliefs of each era. He emphasises the argument between a physiological and a supernatural approach to the disease and stresses the influence of Galen's "humoral" theory on beliefs up until the nineteenth century.

As Galen's theory was so far reaching it should be described in more detail. Galen (AD 130-201) hypothesised two main types of epilepsy, the first of which arose from

a gathering of phlegm or black bile in the ventricles of the brain and was known as "idiopathic" epilepsy. Secondly, he suggested that attacks could begin in some other diseased area of the body which sent harmful vapours to the brain and he called this type of epilepsy "sympathetic". Galen's theory was physiological rather than superstitious and so amongst his remedies were the binding of the limb in which attacks began, blood letting and the expulsion of excess phlegm through surgery.

It is suggested by Temkin that Galen first introduced the word 'aura' to describe an attack which he observed in one patient, beginning in the lower part of the leg and spreading along one side of the body. Another observer was heard by Galen to say that the spreading of the attack was like a cold breeze. This is contrary to the popular belief that the term 'aura' was originally used by a patient of Galen's to describe the gustatory sensation he experienced at the onset of a seizure.

Parallel beliefs at this time included the notion that epilepsy was inflicted by the Gods as a punishment for sins against the Goddess of the Moon. It was also believed by some, that an evil spirit had entered the body of the sufferer who was to be avoided at all costs for fear of being similarly possessed. Such ideas probably led to the use of the term 'the sacred disease' to denote epilepsy and, as Temkin suggests, meant that the sufferer was not

only treated with great awe but also regarded as a social outcast particularly at the time of an attack.

Remedies themselves were therefore often magical, and many related to beliefs surrounding the moon, for example, sufferers were told never to wear or lie on goat skin as the goat was sacred to the Moon Goddess. A great deal of emphasis was also placed on the need for purification and led to such gruesome practices as smearing the lips with human blood.

Even those who, like Galen, believed in a natural cause for epilepsy could not deny that some magical remedies which were supposedly based on past experience, appeared to work. They did however, attempt to provide scientific explanations for these remedies. This, Temkin suggests is why Galen advocated the hanging of a peony root around the neck of one patient hypothesising that it altered the surrounding atmosphere or was in some way absorbed into the body and was not simply an amulet.

According to Temkin the term epilepsy is derived from the Greek word epilambanein meaning to seize or attack. Whilst this term was preferred by ancient Greek physicians over the 'sacred disease' it was probably used to describe the attack itself and not the underlying illness which remained 'sacred'.

During the middle ages Christianity exerted its influence

on medical theories and practices with a prevalence of monastic medicine. Unfortunately, the treatment of epilepsy seems to have taken a step backwards to the pre-Hippocratic era, attacks being regarded as retribution for sin or a consequence of sorcery and possession (Schneble 1985). Such ideas may have been derived from Biblical sources. Matthew, Mark and Luke all give accounts of the healing of a boy who had experienced a seizure. Luke (Ch.9: Vs 37-39) for example, describes how the boy's father pleads with Jesus to heal his son "a spirit seizes him and he suddenly cries out; and it throws him down and convulses him so that he foams, and bruising him sorely; it scarcely leaves him". Luke (Ch.9: Vs.42) goes on to tell how "Jesus rebuked the unclean spirit and healed the boy, and restored him to his father". It is also possible that the remedies favoured during the middle ages found their root in the Bible. According to Mark (Ch. 9: Vs.16) Jesus said after healing the boy, "this kind can be cast out in no way except by prayer and fasting".

The term used for epilepsy in the middle ages was the "falling sickness" or the "falling evil" and was obviously derived from the tendency of sufferers to fall to the ground.

Temkin suggests however, that this term was also used to describe any kind of attack characterised by a fall.

Many Patron Saints of epilepsy appeared in the middle ages, the three wise men for example, because they "fell" before

Jesus. Also, St. Valentine whose name sounds so similar to the German word "fallen".

Ancient superstitions still had their place in the middle ages and astrologers emphasised the role of the Moon and Mars in determining the incidence of attacks. This possibly also partly explains the association of epilepsy with lunacy.

In 1130 the Council at Clermont prohibited monks to act as physicians and medicine gradually fell into the hands of the scholars. The first pediatric textbook appeared in 1472 by a Professor of Medicine in Padua called Paulus Bagellardus. Again Galen's influence became apparent and epilepsy was described as the blocking of the ventricles (Schneble 1985).

In Europe in the 16th century a physician known as Paracelsus introduced a new approach to the 'art of healing'. He saw the work of the physician as a divine service with an emphasis on healing by natural means. He regarded all scientific disciplines as part of the macrocosm with the same forces affecting the planets as affecting the human being. In the case of epilepsy he saw the element of fire as being important and used chemical substances such as vitriol as a remedy (Schneble 1985).

Physicians however, still admitted the possibility of possession being responsible for seizures and attempted to distinguish this from true epilepsy. Talking in

foreign tongues during an attack, for example, was seen as a sign of possession. By now, several causes of true epilepsy had been established namely, sudden fright, injuries to the head, syphilis and scurvy. It had been recognised for many centuries that a seizure could involve only part of the body, but it was not yet postulated that these attacks could actually begin in the brain. An alternative theory came from Charles le Pois in the early part of the seventeenth century. It was believed at this time that the blood contained a watery substance or 'serum' which passed through the walls of blood vessels and gathered in the base of the head. Le Pois suggested that if an excess of serum existed, it could flow into the roots of nerves and cause them to elicit abnormal movements of various parts of the body depending on which nerves were affected. Thus, the idea of vapours arising from a part of the body and then affecting the brain began to loose ground, as did the idea that epilepsy was due to a blocking of the ventricles. Indeed, anatomical evidence began to show that this was not the case and the idea that epilepsy was due to an irritation of the brain by some noxious substance came to the fore.

According to Temkin, by the second half of the eighteenth century the old idea of possession by evil spirits began to disappear. Epilepsy now became closely linked with hysteria, attacks occurring in people who had witnessed others having seizures. The idea that epilepsy was contagious was revived and there were even reports of mass

convulsions. It thus became necessary to separate patients with epilepsy from the insane with whom they had traditionally been hospitalised. This grouping together was fortunate in that it enabled closer study of seizures and a new terminology was developed.

Poupart in 1705 described an attack, which would now be called an absence seizure, in which a patient's speech was arrested for a few seconds and then continued exactly where it had left off. In 1770, Tissot used the terms 'grands accès' and 'petits accès' (Trimble 1983). These terms were interchangeable with the terms used by Esquirol in the early nineteenth century. He used 'grand mal' to describe attacks which included loss of consciousness and generalised convulsive movements, and 'petit mal' to describe any attack which did not include convulsions. A few years later, Calmeil actually used the term 'absence' to describe attacks which consisted of confusion but which were without physical accompaniment (Trimble 1983). At around this time, Galen's 'aura' became the term used for feelings experienced prior to attacks which were recognised as a warning. The term 'status epilepticus' was introduced to describe a series of attacks without interruption and with a poor prognosis. There was increasing use of the term idiopathic epilepsy but it was sometimes called essential epilepsy, ie. without known lesion or cause. Sympathetic epilepsy was still said to originate in a part of the body other than the brain but it was no longer believed to be due to harmful vapours arising from that

part of the body. Instead, it was thought that the origin of the attack was the first part of a reflex arc which then extended along the spinal cord to the medulla oblongata which in turn caused other nervous tissue to discharge and involve other areas of the body. Sympathetic epilepsy was also often known as eccentric epilepsy, (originating outside the central nervous system) or reflex epilepsy. Finally, symptomatic epilepsy was recognised as arising from a cerebral lesion, the seizure therefore being the symptom and not the disease.

In 1860, the National Hospital for the Paralysed and Epileptic at Queen Square was opened. The grouping together of patients made it possible to carry out controlled clinical trials. Reynolds (1861) suggests however, that most of these were fruitless until the introduction of bromide of potassium of which two and a half tons a year was used at the National Hospital by 1875. It was known that bromide produced temporary impotency in men, it was therefore tried as a cure for 'uterine' hysteria in women. Having discovered that it did in fact have an influence on the ovaries it was thought that it may influence seizures which were related to the menstrual cycle. Finally, Samuel Wilks used it in both men and women with epilepsy and bromide of potassium became a recognised treatment (Temkin 1945). Unfortunately, the side-effects included skin rash (acne), headaches, drowsiness, weakness and foul breath.

In the eighteenth and nineteenth centuries many significant advances had been made in the field of neurophysiology. In 1756, Caldini observed the contraction of muscle after stimulation of a frog's nerve with an electric spark and Galvani later stimulated a similar muscle with another nerve from the other side of the frog's body. In 1820, Ampere described the galvanometer and later Ohm clarified the relationship between electromagnetic flow, current and resistance. In 1843, Du Bois Reymond showed how electrical impulses passed down a nerve fibre and six years later recorded the first electromyogram from the human arm during voluntary contraction. By 1852, Helmholtz was able to show how the velocity of these nerve impulses could be measured (Bates 1985).

A Liverpool physiologist, Richard Caton was inspired by these findings and set out to discover whether similar impulses could be recorded from the exposed cortex of the rabbit and monkey after stimulation of any of its sense receptors. Caton found that this was possible and noted at the same time that even without the experimental stimulation the brain still generated feeble electrical currents (Caton 1875).

This latter finding was disregarded to a large extent as scientists at this time were too preoccupied with the localisation of brain function. In relation to epilepsy,

several workers had noted that spasms in certain parts of the body were attributable to lesions in specific areas of the cortex. None however, made such an extensive study as John Hughlings Jackson who lived from 1835 to 1911 and from 1859 onwards was associated with various London hospitals.

Jackson hypothesised four causes for these spasms. Firstly, a localised lesion of the cortex caused, for example, by damage to the regional blood supply. Secondly, a change in the functioning of the nerve tissue itself. Thirdly, a pathological process such as a tumour or syphilis and finally an alteration in the body's equilibrium such as a shock. In 1873, Jackson described epilepsy as "occasional, sudden, excessive, rapid and local discharges of grey matter"(cited in Temkin 1945). He therefore saw all types of seizure as being of focal origin. Jackson also suggested that damaged cells which fired abnormally could cause healthy cells to fire too and would thus spread to surrounding areas. He also described 'dreamy states' which he called uncinete fits, attacks which would now be known as complex partial seizures.

The next significant contribution in this field came from W.R.Gowers in 1881. Gowers was a junior colleague of Jackson and greatly acknowledged Jackson's work although his own approach was rather different in that he emphasised the difference between focal seizures due to a specific lesion, and generalises seizures without observable pathological signs. He studied 1,450 patients mainly at

the National Hospital and described many different types of seizure and their statistical frequency and aetiology (Penfield and Jasper 1954). One of the most important distinctions he made was between true epilepsy and hysterical attacks. Genuine epileptic attacks he called 'functional' and non-epileptic he called 'hysterical'. He also acknowledged the existence of both types of attack in the same patient (Trimble 1983). Today the distinction between epileptic and non-epileptic attacks often proves difficult even with the aid of the EEG. How much more difficult it must have been for Jackson, Gowers and others working with patients at that time. It was not until 1901 that Einthoven developed the first string galvanometer and paved the way for Hans Berger's experiments with the EEG (Bates 1985).

Hans Berger working in Jena was the first to recognise the importance of the brain's ongoing electrical activity. In 1920, Berger made his first, though unsuccessful, attempt at recording from the head of a bald medical student. His knowledge of physics and instrumentation was poor and it was another four years before he obtained successful recordings from electrodes placed over skull defects in patients injured in the first world war. The equipment he used was really designed for ECG recording, the signals it produced were very crude and Berger often had difficulty in distinguishing them from artefact.

Nevertheless, in his 1929 report, Berger showed that

Caton's 'feeble currents' did not arise from cerebral blood flow, muscle artefact, eye movement or cerebral pulsations and two years later he described recordings from the surface of the cortex itself. Subsequent publications concerned the reactivity of the alpha rhythm (which he named), he noted also that the alpha was slower in patients with cerebral lesions but he did not use the terms theta or delta. Although he failed to record a tonic-clonic seizure adequately, he did record post-ictal attenuation and probably also recorded several complex partial seizures. His recordings of 3cps slow activity during absence seizures unfortunately showed no spike components and he suspected he had simply recorded artefacts. Berger also noted inter-ictal discharges and correctly assumed that these signified a tendency to have seizures. In 1933 he published a report concerning a patient with simple partial seizures consisting of jerking of the right hand. He localised these to the left central region and was thus the first person to confirm the theories of John Hughlings Jackson, although Berger himself seems to have been unaware of Jackson's writing.

Unfortunately, much of Berger's work went unrecognised in his own country. Neurologists at the time could not believe that such regular oscillations could represent the activity of an organ as complex as the brain. In addition, the Nazis were rising to power, Berger disliked them and they retaliated by disparaging his work and

forced him to resign from his position as Chairman of the Department of Psychiatry at the University of Jena. Three years later, Berger committed suicide.

Berger's discovery of the electroencephalogram as well as other aspects of his life and work are well reviewed by Gloor (1969).

Elsewhere in Europe, Berger's work was acknowledged and Adrian replicated his findings in 1934 using a Matthews oscillograph. Although it is often said that Berger worked very much in isolation, several letters did pass between himself and Adrian and Matthews showing, amongst other things, that they disagreed on the distribution of the alpha rhythm.

Although unavailable to Berger, the first ink writer for EEG was developed by Tonnes in 1931. In 1936 a five channel system was available, thus in the same year W.Grey Walter described the technique of phase reversal and named delta waves (Bates 1985).

1.3 SEIZURE CLASSIFICATION

It was now possible to observe the characteristic changes in the EEG during various types of seizures and classification therefore became more feasible. Gibbs, Gibbs and Lennox (1938) noted that "a fast rhythm spells grand mal, a slow rhythm psychomotor and an alternating slow and fast

rhythm petit mal epilepsy". They also observed a change of frequency in the EEG in relation to blood sugar and carbon dioxide level and reported the first lobectomy performed on the basis of abnormal EEG activity. Their 'psychomotor' seizures consisted of attacks in which patients appeared to be conscious but did not respond to commands, they performed quasi-purposeful actions and had no recollection of events during the attack on recovery.

Penfield and Jasper (1954) suggested an alternative method of seizure classification based upon the site of origin of attacks in the brain. Focal cerebral seizures (previously termed symptomatic) were said to arise in the grey matter and showed localised spiking or other rhythms. Centroencephalic seizures were said to arise from the "central integrating system of the higher brainstem". These were characterised by discharges appearing simultaneously from both hemispheres such as the 3 cps spike and wave activity of absence seizures or the "bilateral rapid rhythms" which were observed in tonic-clonic seizures.

Between 1964 and 1969 the International League Against Epilepsy sought to devise a classification system based upon; the clinical description of attacks, the EEG during attacks, the inter-ictal EEG, the site of origin and aetiology of attacks and the age of the patient. This system which is described by Parsonage (1983) includes the following. Firstly, partial seizures sometimes with elementary symptomatology, ie. without involvement of

high-level cerebral activity and sometimes with complex symptomatology, ie. with involvement of high-level cerebral activity. Also, partial seizures (with complex or elementary symptomatology) which become secondarily generalised most commonly developing into a tonic-clonic seizure. In all of these partial seizures the EEG abnormality begins in a narrowly limited area of the cortex, together with the observable clinical changes for that area.

Secondly, the 1969 classification includes generalised seizures, ie. seizures without signs of focal onset either in the behaviour of the patient or in the EEG and usually characterised by loss of awareness at the beginning of the attack. Included in this category are; simple absence seizures with impairment of consciousness only, or complex absence seizures in which various behavioural changes such as automatisms (quasi-purposeful movements) or slight jerking are observed. Both types of absence seizure may be accompanied by 3 cps spike and wave activity or variations of this.

Generalised seizures also include; tonic-clonic seizures, myoclonic jerks, infantile spasms, clonic seizures, tonic seizures, atonic and akinetic seizures. Again the EEG discharges are bilateral, synchronous and symmetrical.

Thirdly, the 1969 classification includes unilateral or predominantly unilateral seizures. In these attacks the discharge is wholly or predominantly seen in the EEG over one

hemisphere and the clinical accompaniment is seen on the contralateral side of the body. Consciousness may or may not be impaired.

Finally, a category of unclassified epileptic seizures is included for which insufficient information is available.

This method of classification is still adhered to by many authors and so an adequate understanding of it is obviously desirable. For the purpose of this thesis however, the 1981 classification system has been used (see Appendix 1) for the following reasons.

Firstly, in the 1969 classification 'complex' is used in two ways, firstly to describe partial seizures and secondly in the classification of absences. When partial seizures are referred to 'complex' is used to describe the involvement of higher brain functions, eg. déjà-vu and forced thinking. This definition cannot however, be used in the description of absence seizures which, by definition, involve loss of awareness and therefore the involvement of higher brain functions. Nor can the term 'complex' be ascribed to eyelid flutter or atonia as seen in absence seizures. Therefore when absence seizures are described the term 'complex' is interchangeable with 'complicated' although nowhere in the 1969 classification is this actually stated.

In the 1981 classification, complex is used only to

describe loss of consciousness, ie. "the degree of awareness and/or responsiveness of the patient to externally applied stimuli" (I.L.A.E. 1981).

A second objection to the 1969 classification is the inclusion of infantile spasms with generalised seizures. As Parsonage (1983) points out, this is a syndrome and not a seizure type. Nor is the EEG discharge bilateral, grossly synchronous and symmetrical over the two hemispheres as is defined for generalised seizures.

A final comment on the 1969 classification concerns the inclusion of unilateral or predominantly unilateral group of seizures. As these attacks are limited to such a narrow age group, perhaps they do not warrant a class unto themselves.

The 1981 classification in fact does not use age at all as one of its criteria, it uses only clinical seizure type and the ictal and inter-ictal EEG. The Commission on Classification and Terminology of the ILAE (1981) state the main reason for this is that insufficient knowledge is available to classify seizures by "anatomical substrate, aetiology and age". The 1981 classification is also based on information gained from prolonged EEG recording and video monitoring and is therefore more applicable to a thesis concerning long term ambulatory monitoring. It is not however, without its problems. The term 'atypical absence' for example, requires some clarification.

Gastaut (1973) suggests that this refers to the kind of seizure found in children with Lennox-Gastaut syndrome.

Parsonage (1983) objects to the use of the definition of 'complex' as impairment of consciousness because the neurophysiological basis of consciousness is unclear. He suggests this should for example include some reference to the patients' memory for events which occurred during the attack, as well as his responsiveness to external stimuli.

In conclusion, it is perhaps necessary to reiterate that no classification can be static, it must involve a progression as new knowledge is obtained and that "it is of great importance that for the purposes of communication, unanimity of terminology be attained. This is especially important in clinical research" (ILAE 1981).

1.4 THE DEVELOPMENT OF 24 HOUR AMBULATORY EEG MONITORING

Ambulatory monitoring is the term used to describe the recording of various physiological parameters from subjects in a completely unrestrained environment for prolonged periods.

Traditionally, patients with epilepsy are referred to the EEG department for a basic sixteen channel EEG which lasts approximately 20 minutes. However, the basic EEG

may only become abnormal during an attack or show non-specific abnormalities between attacks and the probability of an attack occurring in such a brief recording period is low. Also some EEG patterns which are present in patients with epilepsy are also present in normal subjects or other medical populations (Turner 1982; Zivin and Ajmone Marsan 1968). Thus, unless an attack is actually recorded in the laboratory, the basic EEG may not provide sufficient additional information to make a firm diagnosis.

One of the ways of overcoming this is to use EEG radio or cable telemetry. However, this involves confining the patient to a limited area for a prolonged period so that he or she remains within the range of the receiver and it therefore usually necessitates hospitalisation. One of the advantages of this method is that the patient can also be video monitored and the record played back, together with the EEG, on a split screen. Additional EEG channels can also be made available for recording from deeper areas of the brain to localise epileptogenic foci in patients who are possible surgical candidates. Detailed observation of attacks via the video recording can also aid the diagnosis. The disadvantage of the technique is that the patient is in an alien environment and the normal pattern of attacks may not be recorded. A separate room is also required in which to carry out the procedure which may make it expensive and impractical for some EEG departments. Thus, the development of techniques for 24 hour ambulatory monitoring has brought prolonged EEG recording within the

scope of routine investigation in many departments.

Before a viable system for ambulatory monitoring could be developed, two major problems had to be overcome. The first was the minimising of artefact from external noise and patient movement and the second was how to accomplish adequate data reduction.

One of the earliest attempts to provide a truly ambulatory system (as opposed to telemetered EEG) was made by Ives and Woods (1975) in Montreal. They modified Marson and McKinnon's (1972) 4 channel portable analogue ECG cassette recorder to record EEG by using preamplifiers with a smaller gain. This recorder weighed 400 grams and with a tape speed of 2mm/sec., a C120 cassette would last for 24 hours. The preamplifier pack weighing 10 grams was placed just below the patient's collar and a 4 foot cable connected this with the recorder. Thus, the amplifiers were placed as close to the origin of the signal as possible and lead movement artefact was reduced.

The recording was played back at 60 times real time and written out on an ink jet EEG machine with a paper speed of 150mm/sec., thus a compressed record was obtained at 2.5mm/sec.

This method of playback is adequate for the recognition of high amplitude paroxysmal discharges such as spike and wave activity which stand out against the background

EEG but less well defined abnormalities or dubious segments of recording would have to be written out at normal paper speed (30mm/sec.). Only ink jet EEG machines have sufficient paper speed and a high enough frequency response of the write-out to allow this. In order to mark the record so that significant events could be located and written out in real time, Ives and Woods asked patients to unplug the input signals from the recorder for two minutes, fifteen minutes after recovering from any attack allowing the segment of blank tape to be located on the printed record.

At around the same time another system was being developed at the Stanford Research Institute in the United States of America (Sato, Penry and Dreifuss 1976). This consisted of a head harness containing the preamplifiers and a vest containing the drive amplifiers, analogue to digital converter and a modified cassette recorder, with a total weight of 5lbs. The tape speed was 4mm/sec. and using a C120 cassette the tape would last for 12 hours only. The use of digital recording enabled Sato et al. to achieve a larger dynamic range than the Ives and Woods recorder which distorted signals above 200uV. Playback involved transferring information from the cassette tape to IBM compatible tape and then onto an EEG machine either in real time or eight times real time. The main disadvantage of the recorder was its weight which made it uncomfortable to wear for prolonged periods and its bulkiness which made it cosmetically unacceptable.

An alternative method of arranging the preamplifiers was suggested by Apple and Burgess (1976). They encased them in a small plastic cup (1.72cm. in diameter) together with the recording electrodes. This technique obliterated lead movement artefact and reduced noise. They used an Oxford Medilog cassette recorder with analogue a.c. bias recording, which had previously been used for ECG monitoring (Cashmann and Stott 1974). They also developed an automated analysis technique which eliminated normal or artefactual sections of the recording and "flagged" possible abnormal sections which could then be written out and examined by the electroencephalographer. Unfortunately, the "active" preamplifying electrodes were very expensive and one would assume that such a method of analysis would have several problems.

In 1978, Quay, working at the National Hospital, produced resin coated preamplifiers which could actually be glued onto the scalp close to the electrodes and were small enough to be hidden beneath the hair. These amplifiers were put into use with the Oxford Medilog recorder (now modified for EEG recording) and formed the first really viable system for 24 hour ambulatory EEG monitoring.

This still left the problem of playback to be overcome. Finally, Oxford Medical Systems produced the PMD 12 visual replay system (Figure 1.1) and clinical trials were carried out at the Park Hospital (Stores, Hennion and Quay 1980). Four channels of recorded data are displayed on a 12 inch screen and can be viewed at 20 or



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FIGURE 1.1 4 CHANNEL VISUAL REPLAY SYSTEM

60 times real time in either 8 or 16 second segments. The display can be halted for closer inspection and can also be backpaged by 16 seconds.

One of the EEG channels on the recorder can be sacrificed for a time code channel which also incorporates an event marker and is operated by the patient pressing a button on the recorder. A clock is situated on the replay deck and increments every minute as long as a time code has been recorded on the tape. Alternatively, one channel of ECG can be recorded and also various other physiological parameters.

Other methods of playback and display include a Disa replay deck with a speed of 62.5 times real time with 5 segments of EEG being replayed in succession on a video monitor (Callaghan and McCarthy 1981). Docherty (1981) used a Datalab 4000 as an analogue to digital converter in order to display tapes on an oscilloscope.

Four channel systems are now widely used in many EEG departments throughout the world and although they overcome the two major problems originally encountered, the limitation to only four channels of recorded data presents the problem of inadequate scalp coverage. This therefore necessitated the development of an 8 channel recorder and visual replay.

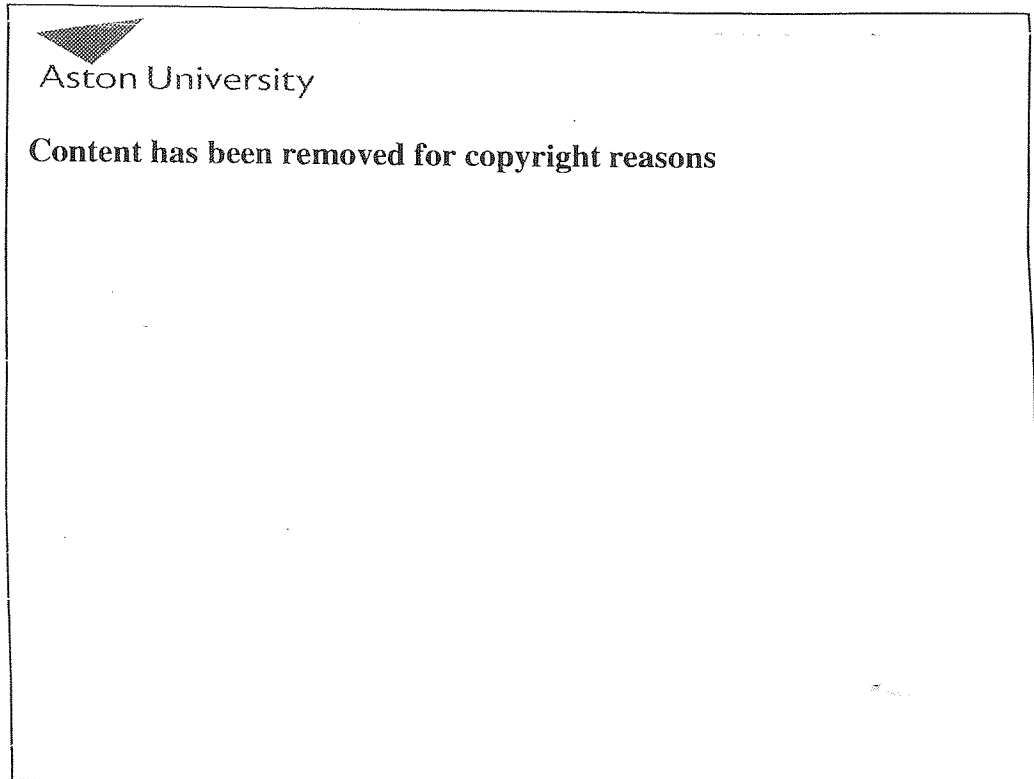
One of the earliest 8 channel systems was described by Sato, Penry and Birch (1978). This was a digital system

which would record for up to 12 hours and was said to provide a truer representation of the original signal than the analogue recorder described by Ives and Woods (1975).

Other portable devices have consisted of systems which only record when the event button is pressed. These have a buffer memory which will enable up to two minutes pre and post, the pressing of the event button to be saved for later replay (Ives 1982). Ives and Woods (1979) however, found that 30% of events recorded from surgical candidates with partial seizures were subclinical, ie. they were EEG events only. As they point out such events would not be recorded on buffer memory systems.

An 8 channel system which records continuously was eventually developed by the same manufacturers as the PMD 12 replay. Clinical trials were again carried out at the Park Hospital and a more efficient playback system was developed to be used with an 8 channel recorder (Figure 1.2). In order to obtain 8 channels of recording on a 4 channel cassette tape a method of 'multiplexing' had to be used. This method compresses several seconds of EEG from one channel onto one track of the tape followed by the same time segment of the next channel and so on until brief sections of EEG from several channels are recorded on one track. The next time segment is then taken from the first channel and so on. In this way one

FIGURE 1.2 8 CHANNEL VISUAL REPLAY SYSTEM AND RECORDER



track of tape can contain data from several different EEG channels. The replay system then decodes the signals back into the correct order.

Recent technological developments have led to the return of the preamplifiers into the recorder itself. Lead movement and noise artefacts are now minimised by the use of an active screening technique. The electrodes themselves are now simply plugged into the preamplifier leads at a small collar which is worn around the patient's neck. A comparison between this method and the head mounted preamplifiers is made in Chapter 3.

CHAPTER 2

LITERATURE SURVEY

Fidelity of Recording

The description of waveforms in terms of frequency, amplitude and morphology is critical for EEG interpretation and reporting. It is therefore important to ensure that any new method of recording produces a true representation of EEG phenomena.

Declerck, Martens and Schiltz (1982) point out that waveforms larger than 200uV may be distorted and cut off when recorded on the ambulatory cassette EEG. This could have important implications on the recording, for example, of spike and wave activity. These authors also found that even in favourable conditions the noise level on the recorders reached 4% of the EEG signal (in most EEG recorders the noise level is 2% of 100uV signal). They therefore expressed concern about the possible difficulty in distinguishing between different types of low amplitude activity such as that found during waking and drowsiness. Further investigations at different points in the system showed that only signals of a higher frequency than 25 c.p.s. would be suppressed by any great degree. In comparison to a direct recording of spike and wave activity on an ink jet EEG machine however, Declerck et al. (1982) found much less signal distortion of the ambulatory recording than had been expected. They finally concluded therefore, that signal distortion was not a problem.

Riley and Peterson (1983) made a similar comparison between sleep recordings made in the patient's own home using telephone polysomnography, recordings made using the ambulatory cassette and recordings made on an EEG machine in the laboratory. They found that all methods were equally as satisfactory for sleep stage scoring. However, the ability of the ambulatory recorder to record submental muscle activity was inferior to the other two methods.

Ebersole and Leroy (1983) used the same electrodes to record both the telemetered EEG and the ambulatory EEG on a continuous polygraphic write-out. They concluded that "the output of cassette recorder amplifiers was of exceptional quality and almost indistinguishable from the cable telemetry record". They comment that when there was movement artifact in the recording the cassette recorder provided a superior quality of recording due to a lack of lead movement between the electrodes and on-head pre-amplifiers. When they wrote the EEG out via a playback unit however, Ebersole and Leroy did find some signal distortion and a lowering in the high frequency response. They compensated for this by using a 0.05 sec. time constant on the EEG machine. In conclusion they appear to be in agreement with Declerck et al. that signal reproduction is not a major problem with ambulatory recording.

Montage Design

It has been suggested that the limitation of 3 or 4

recording channels could be a major problem with ambulatory monitoring, although Leroy and Ebersole (1983) have shown that with careful montage design this need not be true. They used 16 channel telemetry and combined an 8 channel standard montage with various experimental 3 channel montages. They found that a montage including the positions T5-F7, F7-F8 and F8-T6 or P3-F3, F7-F8 and P4-F4 would detect a high percentage of inter-ictal events.

With the advent of the 8 channel recorder montage design has become less of a problem. Three and 4 channel recorders are still widely used however, and since most of the published data concerns 3 and 4 channel recordings, it therefore requires some discussion.

Several important decisions must be made when choosing an appropriate montage. To a large extent these depend on the reason for which the patient has been referred. Figures 2.1 and 2.2 show montages designed by various authors and the type of referral for which they have been used.

The first important decision which must be made is how many EEG channels should be recorded and whether other parameters should, in addition, be recorded. Several authors (Stores 1979, 1980; Green, Scales, Nealis and Ashley 1984; Chai-Wan-Lai and Ziegler 1981) obviously place much importance on accurate time/event information when the question being asked is "are attacks epileptic?".

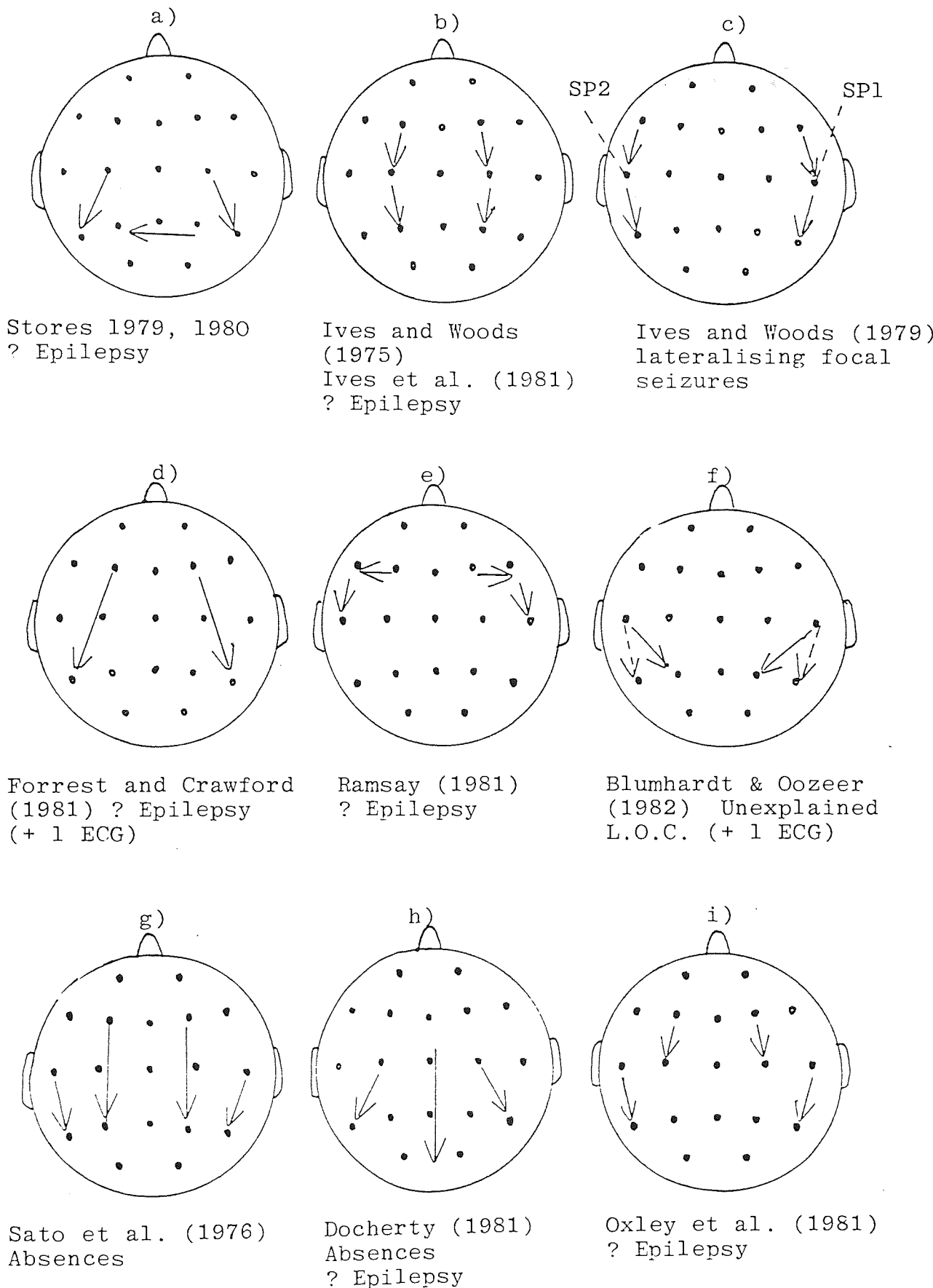
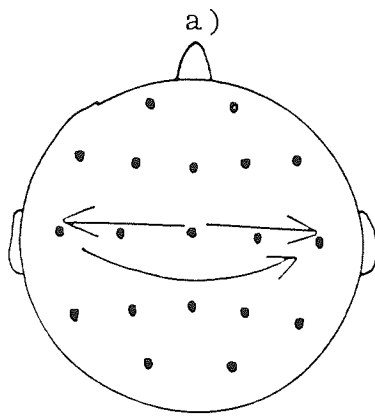
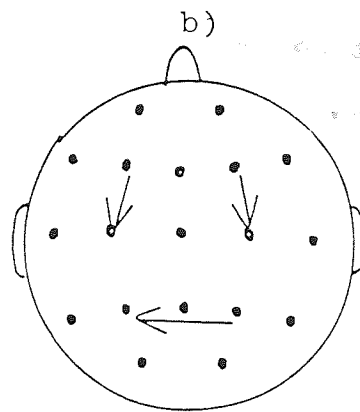


FIGURE 2.1

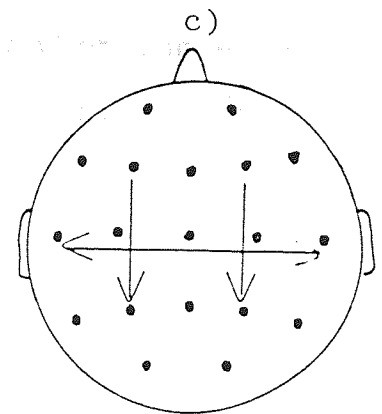
MONTAGES USED BY OTHER AUTHORS



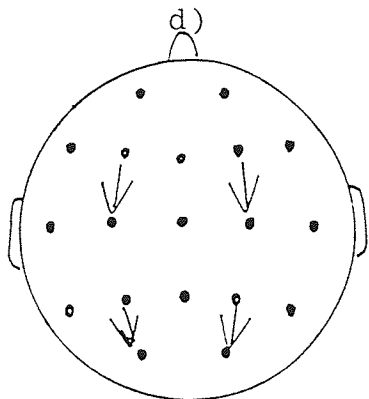
Green et al. (1984)
'blackouts'
(+ 1 ECG)



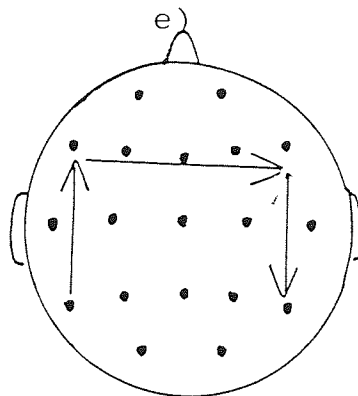
Blomquist and
Zetterlund (1985)
Absences



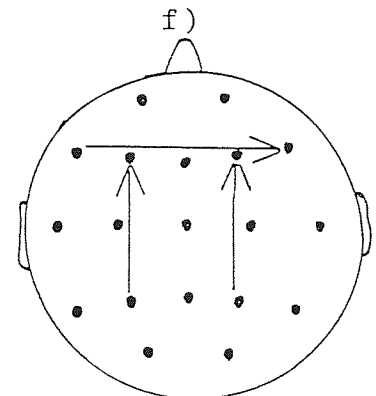
Lai and Ziegler (1981)
Syncope (+ 1 ECG)



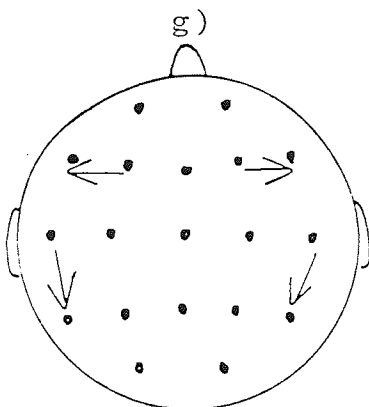
Declerck et al.
(1982)
Abnormalities in
sleep



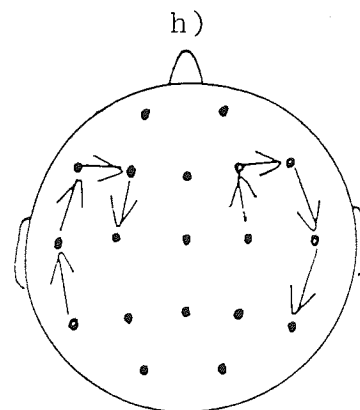
Leroy and Ebersole
(1983)
Anterior and general-
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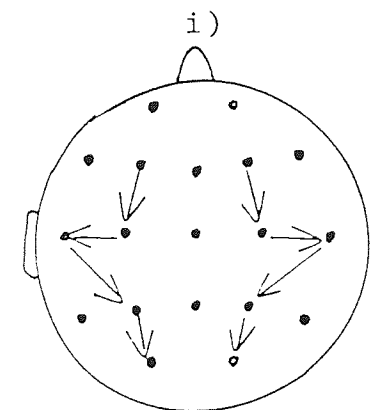
Leroy and Ebersole
(1983) Frontal and
generalised
discharges



Leroy and Ebersole
(1983) Anterior
and generalised
discharges



Ebersole and
Bridgers (1985)



Stores (1985)
? Epilepsy

FIGURE 2.2

MONTAGES USED BY OTHER AUTHORS
CONTINUED

Accurate location of events is necessary when there is a possibility that the EEG will remain normal during attacks, or will show only very subtle changes as in some partial seizures (Klass 1975). As Oxley and Roberts (1981) have pointed out, a non-standard event marker is available for the fourth EEG channel which consists of a high amplitude burst of 50 c.p.s. activity. This however, in our own experience, is sometimes difficult to locate even if pressed several times, if the background EEG is high amplitude and if the time counter on the playback itself is not very accurate.

An accurate time code is also necessary when circadian periodicities in abnormal activity are being examined as carried out by Burr and Stephan (1981) for example. The correlation of seizure activity with environmental factors (Stores and Lwin 1981), also requires an accurate time code so that abnormalities can be correlated with activities on a daily diary sheet.

The necessity to record other physiological parameters also dictates the number of EEG channels to be used. Blumhardt and Oozeer (1982) made a study of patients with unexplained loss of consciousness using only 2 EEG channels, the electrocardiogram (ECG), and one time/event channel in order to detect any cardiac arrhythmias during attacks. One must question however, whether Blumhardt's recent observation that cardiac irregularities often precede genuine seizure activity (Blumhardt et al.(1986) arises simply from a lack of scalp EEG representation.

Stores and Lwin (1981) attempted to use ECG as a measure of emotionality in children so that this could be correlated with abnormal discharges. Unfortunately, there were too many other variables acting on the ECG to provide accurate information.

Other authors such as Docherty (1981) incorporate an electrooculogram (EOG) into their montages. This can be useful for scoring sleep stages and also can help in distinguishing genuine slow activity from eye artifact. Often however, the obvious morphology and distribution of eye artifacts makes it unnecessary to allot a particular channel to it.

Blumhardt and Oozeer (1982) suggest the use of an accelerometer to monitor body movements during attacks so that artefacts arising from this can be distinguished from seizure activity. They also suggest that an ECG channel can perform a similar function. Unfortunately, genuine seizures are also often accompanied by massive body movement artefacts which obscure the EEG. The pre and post-ictal record is therefore of paramount importance, in which case the body movement channel might more advantageously be used for EEG.

Kayed, Hesla and Røsjø (1979) have totally dispensed with the EEG channel and scored sleep using EOG, electromyogram (EMG) and body movements. This would not however, be sufficient if abnormalities were to be detected in the EEG as well as abnormalities in sleep structure.

One other possible physiological parameter which has been suggested is blood pressure monitoring, particularly in cases of possible syncope (Graf, Brunner, Weber, Auinger and Joskowicz 1982).

Finally, Ives and Woods (1979) used sphenoidal electrodes referred to T4 or T3 to lateralise focal discharges in patients with known partial seizures.

The second decision which must be made about montage design is the choice of electrode positions. Again, this may depend on the reason for referral. When anticonvulsant monitoring in patients with sub-clinical generalised spike and wave discharges is carried out any montage will adequately record the abnormality, although Leroy and Ebersole (1983) suggest that channels placed parasagittally (Figure 2.2 (f)) are marginally superior to temporal channels. As Declerck et al. (1982) have pointed out however, the limitation to 3 channels, although adequate to detect spike and wave activity, is inadequate to provide a judgement as to the synchrony or symmetry of the discharges, particularly when the morphology changes during sleep.

When the question asked is; "are attacks epileptic?", a different montage may be required. Unfortunately, the areas of the scalp which are most likely to show abnormality during attacks are also those which record much movement artifact. Leroy and Ebersole (1983) assessed retrospectively the frequency of inter-ictal EEG abnormalities occurring in different areas of the scalp EEG and

found that 32% of abnormalities were generalised and 54% were in anterior temporal and frontal regions. Posterior temporal and parieto-occipital abnormalities were relatively rare. Stores (1986) however, has pointed out that Leroy and Ebersole's study included only adults, whereas in children the distribution of abnormalities may be different.

There is therefore an apparent need to balance scalp coverage with artefact minimisation. Stores (1979, 1980; Figure 2.1a) does this by referring a central electrode to a posterior temporal electrode, although for adults an anterior or mid temporal electrode may increase the likelihood of recording abnormalities. Our own solution has been to deviate slightly from the 10/20 system (Jasper 1958) and use the montage shown in later sections. This montage includes anterior and mid temporal regions without picking up excessive eye artifact or muscle from the jaw. Other authors (Figure 2.1e) and 2.2e) and g)) are obviously of the same opinion and retain anterior and frontal derivations.

The need for adequate monitoring of the alpha rhythm again, must be offset with the possibility of recording abnormalities from frontal and anterior temporal regions and it can be seen that some authors including ourselves prefer to retain a posterior electrode position for this purpose (Figure 2.1h). Alternatively, as can be seen in Figures 2.1a) and 2.2b) some authors prefer to use a parietal channel.

When 4 channels of EEG are used, which is often the case when seizures are known to be genuine but lateralisation is required (Ives and Woods 1979), channels are obviously placed symmetrically. When 3 channels are utilised however, trans-hemispheric recording is often used, for example, the positions P4-P3. The possibility of equipotentiality existing between electrodes could however cause problems and we have preferred to limit the third channel to one hemisphere only.

An obvious guide to the positioning of electrodes is the basic EEG. If this is asymmetric it can provide a guide for the positioning of the third channel. If focal abnormalities are seen in the basic, electrodes can be positioned over areas of maximal abnormality as suggested by Lai, Strong, Eeg and Ziegler (1981).

Cosmetic acceptability must also play a part in montage design, particularly when patients are sent home with the apparatus attached. This often therefore precludes the use of an EOG channel or channels covering frontal pole derivations.

The final decision to be made when positioning EEG channels is how acceptable to the interpreter is the recording obtained? The double spacing of electrodes can produce higher amplitude traces which are alien to some electroencephalographers, a factor which Leroy and Ebersole (1983) appear to disregard. Furthermore, the combination of single spacing and double spacing, eg.

Figure 2.1g) could cause confusion, particularly if inferences are to be made about the location of focal discharges. Faced with a completely different recording environment and a different set of artefacts to that of the basic EEG, we felt that the ambulatory recording obtained, should appear as similar to the basic EEG as possible.

Replaying Ambulatory EEG Recordings

Acceptability of the montage to the interpreter must also be taken into account when replaying tapes. Ebersole and Leroy (1983) take advantage of the concept of phase reversal to aid the reviewer to pick out abnormalities and also to distinguish them from eye artefacts. When recording 8 channels, electrodes are positioned to provide a mirror image symmetry on the playback screen. We however, have found eye movements and sleep phenomena easily interpreted if presented as the familiar in-phase signals one finds in a basic EEG recording. Commonly it is found that genuine focal abnormalities phase reverse and the attention of the interpreter is immediately brought to them since they are the exception rather than the rule.

Eight channel montage design must take particular account of where channels are positioned on the screen so that areas most likely to show abnormality are easily viewed.

In a direct comparison of 3 and 8 channel recordings

(using the same electrodes) Ebersole and Bridgers (1985) found that 3 channel recordings more often produced false positives, (artefacts misinterpreted as inter-ictal abnormalities) and 8 channel produced more false negatives, possibly due to the inability of the reviewer to take in all of the information on the screen. These misinterpretations however, concerned inter-ictal and not ictal events, and one must question the importance of the inter-ictal EEG particularly when so few, if any, 24 hour control studies of normal subjects have been carried out.

Eight channel montage design is less problematical than 3 channel and perhaps should be more concerned with the preference of the reviewer and the positioning of channels on the screen, as well as the minimising of artefact. One of the montages preferred by Stores (1985) can be seen in Figure 2.2.j).

Methods of analysis appear to vary from author to author. In some instances (eg. Ramsay 1981) tapes are reviewed by the EEG technician and then re-examined by the electroencephalographer. Such a method obviously provides useful feedback to the persons involved in the application of the apparatus. Other authors (eg. Ebersole and Leroy 1983) imply that analysis is carried out only by the electroencephalographer. Graf et al. (1982) review the tapes on the playback unit and then write out relevant sections onto an EEG machine, if no relevant sections

are present samples of the tape are taken at hourly intervals. The ECG traces incorporated into their recordings are analysed by two cardiologists.

A protocol for replaying tapes has been suggested by Ebersole and Leroy (1983). They advocate replaying at 60 times real time during waking as ictal events are detected easily by sound and inter-ictal events are usually obscured by excessive muscle artifact. A lower replay speed is recommended for periods of quiet wakefulness and light sleep, continuing into the first REM cycle in order to detect inter-ictal events. In the early morning with the transition from sleep to wakefulness they suggest that abnormalities are again more likely to occur and tapes are therefore replayed slowly.

Patient Selection

Dunstan (1985) suggests that the ambulatory EEG should only be performed if the basic EEG is non-specific or if attacks occur at least once a week; he says "such an approach would save EEG departments much unproductive work and reduce the risk of the technique falling into disrepute for a low yield". The value of the basic EEG and other techniques compared to the ambulatory EEG will be discussed in the following section. However, selection of patients for investigations is perhaps best mentioned under the technical aspects of recording.

Blumhardt and Oozeer (1981) point out that in patients not

selected for frequently occurring attacks, only 16% experienced significant events during recording. Table 2.1 shows the percentage of patients who experienced attacks in studies by various authors. Few authors clarify whether patients were actually selected on this basis, but those who recommend either one attack or more should be occurring per day (Davidson et al. 1981 and Bachman 1984) or one or more attacks per week (Forrest and Crawford 1981) seem to have achieved high success rates. Those studies of presumably unselected patients (Graf et al. 1982 and Ramsey 1981) have recorded few attacks. Some authors however, (eg. Callaghan and McCarthy 1981 and Ebersole and Leroy 1983) feel that even if no attack is recorded the inter-ictal EEG can provide useful diagnostic evidence.

Several authors recommend that recording should be prolonged for several days. Stores, Brankin and Crawford (1982) report a continuous recording for 14 days in one patient. Table 2.1 shows that Oxley et al. (1981) presumably prolong recordings until attacks have been recorded and therefore achieved a 100% success rate. The length of recording obviously depends on the pressure of referrals and the availability of equipment, the mean length of recording in general appears to vary between 1 and 2 days. It would therefore appear necessary to select patients on the basis of frequently occurring attacks and to offset this with a slightly longer recording duration to obtain maximum benefit from an ambulatory

AUTHOR	TOTAL PATIENTS	ATTACK FREQUENCY	RECORDING PERIOD	RECORDS WITH ATTACKS	ATTACKS ABNORMAL	ATTACKS NAD	OTHER
Stores (1980)	37	N.G.	mostly 1 day	9 (24%)	6	3 (33%)	-
Ramsay (1981)	463	? unselected	mean 1 day	31 (7%)	16	15 (48%)	-
Docherty (1981)	89	N.G.	N.G.	48 (54%)	33	14 (29%)	1 cardiac
Oxley et al. (1981)	18	N.G.	most 1 day a few up to 9 days	18 (100%)	7	6 (33%)	3 inter-ictal abns 2 mixed
Callaghan & McCarthy (1981)	46	N.G.	All 1 day	N.G.	6	N.G.	3 cardiac 15 inter-ictal abns
Davidson et al. (1981)	22	recommend >1 a day	mean 1 day	17 (77%)	6	9 (53%)	1 cardiac 1 mixed
Ives et al. (1981)	40	N.G.	N.G.	22 (55%)	5	17 (77%)	-
Forrest and Crawford (1981)	76	recommend 1 a week	mean 2 days	38 (50%)	20	18 (47%)	-
Blumhardt & Oozeer (1981)	68	unselected	1 - 4 days	11 (16%)	1	7 (64%)	1 cardiac 2 equivoca

TABLE 2.1 DETAILS OF INVESTIGATIONS CARRIED OUT BY OTHER AUTHORS

AUTHOR	TOTAL PATIENTS	ATTACK FREQUENCY	RECORDING PERIOD	RECORDS WITH ATTACKS	ATTACKS ABNORMAL	ATTACKS NAD	OTHER
Callaghan & McCarthy (1982)	48	N.G.	4 hours to 5 days	37 (77%)	18	10 (27%)	5 cardiac 4 mixed
Graf et al. (1982)	22	? unselected	N.G.	3 (14%)	1	2 (67%)	-
Bachman (1984)	38	recommend 1 a day	N.G.	20 (53%)	6	14 (70%)	-
Berkovic et al. (1984)	87	N.G.	mean 2 days	40 (46%)	22	12 (30%)	1 inter-ictal 1 equivocal 4 miscellaneous

TABLE 2.1 (continued)

N.G. = Not Given

EEG service.

It is often suggested that the recording environment might have some influence on the occurrence of attacks. Sato, Penry and Dreifuss (1976) certainly demonstrated that home and hospital environments could have a differential effect on the pattern of occurrence of absence seizures in some patients. Stores and Lwin (1981) further demonstrated that worry, boredom, drowsiness, physical activity and even hunger could increase the amount of seizure activity in the ambulatory EEG. It is therefore important to assess the effect of the recording environment on the likelihood of attacks occurring. It may be beneficial for some subjects to be recorded at home, work or school as this may increase the possibility of recording a typical attack.

The recording environment should also therefore be considered in order to optimise the value of ambulatory EEG investigations.

Finally, patient acceptability must be considered when selecting subjects for recording. Hall (1981) describes the use of a 3 channel recorder in severely handicapped children. Although close supervision was required, there was no attempt to remove the electrodes or cause wilful damage to the apparatus. Eyre and Crawford (1981) have also used an ambulatory recorder to aid in the diagnosis of abnormal behaviour in seriously ill neonates. They obtained successful recordings in all 14 babies investigated.

Artefact recognition

EEG recording from ambulatory subjects has given rise to a new realm of EEG artefacts far more sophisticated than those arising from traditional basic laboratory recordings. Often in the laboratory, subject movement is concomitant with lead movement artefact and the entire EEG is obscured by the blocking of the amplifiers. The head mounted pre-amplifiers (Quy 1978) used for ambulatory recording however, preserve the record and produce activity which can at times appear disconcertingly similar to seizure activity.

The perception of the problem of artefact recognition seems to vary from author to author.

Stores (1980) for example says "artefacts did not appear to be any more of a problem when interpreting the results than in interpretation of normal EEGs". Conversely, Blumhardt and Oozeer (1982) suggest "identification of the causes of artefacts is often impossible even when accurate diaries are obtained from healthy subjects". Table 2.1 also shows the number of recordings during which the EEG during attacks was equivocal.

Table 2.2 shows the number of recordings lost by other authors due to technical problems. Technical problems may arise from three main sources; these are well reviewed by Blumhardt and Oozeer (1982). Firstly, artefacts may arise from idiosyncrasies of

TABLE 2.2

<u>AUTHOR</u>		<u>PERCENTAGE OF RECORDINGS LOST OR IMPOSSIBLE TO INTERPRET</u>
Ives and Woods	(1975)	'virtually artifact free'
Ives, Wilkins, Jones, Andermann and Woods	(1976)	0.5%
Abraham, Docherty and Haslam	(1977)	15% (adverse conditions)
Ives and Woods	(1979)	5% (of events)
Stores	(1980)	8%
Forrest and Crawford	(1981)	3%
Davidson, Fleming and Kettles	(1981)	1%
Ramsay	(1981)	4%
Declerck, Martens and Schiltz	(1982)	1978 - 24% 1982 - 3%
Blumhardt and Oozeer	(1982)	1.4%
Finnegan, Abraham and Docherty	(1985)	3.5% (adverse conditions)

the recorder and playback themselves. A faulty drive belt, for example, causes periods of fast activity alternating with paroxysms of very slow activity. If a time code has been recorded on the tape this fault can be identified by examining the time marker which will show corresponding changes in frequency. Ives and Woods (1979) note that several of their recordings were lost due to battery failure, cassette jamming, and broken wires. Battery failure can occur even with previously unused batteries due to a restricted shelf life or unfavourable storage conditions. Cassette jamming only usually occurs if a tape has been incorrectly inserted so that the tape catches around the incorrect spool. Another fault which has been found in our own laboratory is the disappearance of the EEG and periodic appearance of the time code on the EEG channels. The source of this problem proved to be the absence of two small sponges which were usually located beneath the recorder lid and keep the cassette in position when the recorder is vertically placed around the patient's waist.

Broken wires can occur if the lead is accidentally caught on door handles etc. and this usually results in a completely flat channel. A single broken or disconnected electrode however, can produce a pseudo-alpha rhythm at around 10 c.p.s. which can be seen later, in the section dealing with artifacts produced by normals and patients in the present study.

Ives and Woods (1975) also note a large D.C. drift on

the recording which they found to be caused by dirt on the tape recording heads.

One method of avoiding such problems is to check the recording at intervals throughout the day. This is obviously only possible in a hospital or clinic environment. Fortunately, such problems are now exceedingly rare.

The second source of artefacts is poor electrode connections and high resistances. Often artefacts resembling sharp waves are produced in the recording as described by Jayakar, Patrick, Sill, Shwedyk and Seshia (1985).

In our experience however, these artefacts are usually identifiable due to the presence of an extremely sharp initial slope and a slower more irregular second phase similar to a D.C. voltage shift. As Blumhardt and Oozeer point out it is essential to examine the whole 24 hour tape for continuous performance of all channels, often the artefacts described above co-exist with periods of low amplitude 50 c.p.s. interference.

When electrode resistances are high or unbalanced, any artefacts caused by external sources are accentuated. This is commonly seen in the morning when patients are nearing the end of the 24 hour period. Unfortunately, this is also often the most likely time for certain types of attacks to occur (Janz 1974).

The third cause of artefact is from the patient himself or from external interference. Blumhardt and Oozeer (1982) describe 'switching transients' and 50 c.p.s. hum caused by electric blankets. We have noted very high amplitude 50 c.p.s. interference arising from an ambulance radio.

Artefacts arising from the patient are obviously the most important and also often the most difficult to interpret. Some, such as pulse, eye movement, swallowing and ECG artefact are similar to those found in the basic EEG and so are easily recognised. The recognition of others however, requires strict logging of daily activity on a diary sheet. Unfortunately, not all patients are able to comply with this or simply forget.

Blumhardt and Oozeer have described many of these artefacts which again are shown in a later section. Scratching artefacts were found to be associated with short bursts of rhythmic slow activity and muscle spiking. This was usually seen unilaterally with muscle potentials over the opposite hemisphere. Vigorous scratching near the vertex however, would cause symmetrical slow rhythms. Strange sharp elements were also produced by a mixture of scalp and electrode movement. These often arose in combination with 1-5 c.p.s. activity associated with; walking, running, skipping, shaking or nodding the head, rubbing the scalp, washing the face or turning over in sleep. The use of electrodes mounted

in a plastic cup or electrodes with a felt pad and resin coated upper surface reduced the sharp elements but did not prevent the artefacts. Berkovic et al. (1984) have even used crepe bandages to keep the apparatus attached and prevent scratching, although this reduces cosmetic acceptability.

Artefact recognition becomes of paramount importance during the recording of attacks. Blumhardt and Oozeer looked at artefacts created by a control group of patients with definite epileptic seizures. In some, muscle activity completely obscured the EEG abnormality. Some complex partial seizures were difficult to interpret due to chewing automatisms, and post-ictal slow activity was not always present. Slow turning of the head was found to mimic post-ictal slow activity and when attacks occurred in sleep post-ictal slowing was impossible to differentiate from slow wave sleep.

Possible non-epileptic attacks were often found to be associated with gross movement artefact and muscle activity. If movements were less vigorous however, artefacts could appear similar to the EEG abnormalities seen in the control group.

Blumhardt and Oozeer advocate the use of an ECG channel to aid in the differentiation of genuine abnormal EEG activity and movement artefact. Artefacts appear as similar changes in the ECG channel to those on the scalp.

However, as previously mentioned, similar artefacts occur during genuine seizures and therefore it is important to examine the spread of the abnormal discharge and the change in its frequency which requires as many EEG channels as possible.

In the present study, attacks were examined before the electrodes were removed and if doubt existed the patient was asked to simulate the movements he makes during attacks. This was usually possible as patients were often accompanied by persons who had previously observed their attacks and could judge the similarity of the simulated attack to the genuine one.

Fortunately with the advent of 8 recording channels, artefact recognition is less of a problem. In their comparative study, Ebersole and Bridgers (1985) found that 3 channel recordings were associated with false positive results (artefacts mistaken as ictal events) in 2 out of 30 recordings. In a further 3 recordings, artefacts were classed as 'equivocally abnormal'. The same records however, were classed as 'equivocally abnormal' in only one instance when the 8 channel recordings were examined.

Many studies said to evaluate ambulatory monitoring examine only the number and types of cases in which it is known to be useful, eg. Declerk, Martens and Schiltz (1982); Smith (1981). Truly comparative studies, ie. those which compare ambulatory monitoring to standard techniques are rare.

Perhaps the most relevant question for many EEG departments is how often does the ambulatory EEG provide additional information to the basic EEG? If the extra gain of information was low, then the procedure may be too time consuming to be worthwhile.

Zschocke, Hunger and Alexopolous (1982) compared basic EEG results with 48 hour ambulatory EEG results in 72 patients. Unfortunately, they give no details of how many patients actually experienced attacks and one can only assume that their results are based upon inter-ictal abnormalities. In patients in whom there was no doubt about the diagnosis of epilepsy (n = 24) 13 showed epileptic phenomena in a recent basic EEG, whereas 20 showed abnormalities during 48 hour ambulatory recording. Therefore one and a half times as much information had been gained from the ambulatory EEG over the basic EEG. When past EEGs were examined however, 20 patients had shown an EEG abnormality at some time.

Zschocke et al. then looked at a second group of patients in whom epilepsy was strongly suspected. In this case they found that 7 showed epileptogenic abnormalities during one

basic EEG and 10 on ambulatory EEG so there was again an increase in information of just under one and a half times one basic EEG.

Finally, they examined results of patients in whom seizures were unlikely to be epileptic. No patient in this group had a past or present basic EEG showing epileptogenic activity, and none showed such abnormality during 48 hour recording.

Therefore it would seem that for patients with epilepsy the ambulatory EEG can provide about 1.5 times as much information as the basic EEG. Further extrapolation of Zschocke et al.'s. data reveals interestingly, that 46% of patients with epilepsy will have one basic EEG which is normal or non-specifically abnormal. When all past EEGs are taken into account this figure drops to 36%. It would appear therefore, that an unspecified number of repeat EEGs can increase the amount of information 1.3 times over just one EEG.

Zschocke et al. also show that in patients with genuine seizures abnormality was found in both the basic and the 48 hour EEG in 83%. Conversely, in patients strongly suspected of having non-epileptic attacks all showed no abnormality in either investigation. They suggest therefore that these criteria could be used to aid diagnosis of untreated patients. Unfortunately, it is not entirely clear whether the basic EEG results in these groups were taken as part

of the provisional diagnosis, if this were the case the results would obviously be invalid.

Bechinger et al. (1982) compared the ambulatory EEG with the basic EEG and the basic EEG after sleep deprivation. Again, no information is given about the number of patients who experienced attacks but 11 of 18 patients showed spike and wave, sharp waves or spikes in the ambulatory EEG.

Only 2 and 3 patients respectively however, showed such abnormalities during the basic and sleep deprived EEG. The ambulatory EEG was therefore around three and a half times more helpful than even the sleep deprived basic EEG.

Finally, Ramsay (1981) also compared results of ambulatory EEG recording with basic EEG recording. Thirty-one patients actually experienced attacks during ambulatory recording, compared to 3 during basic EEG recording (10.3 times as many). In 46 of 401 patients further information was gained from the inter-ictal ambulatory EEG over the basic EEG (11%).

In summary, between one and a half times and ten times as much information can be gained from the ambulatory EEG when compared to the basic EEG depending on whether emphasis is placed upon ictal or inter-ictal patterns. These studies include patients who were largely unselected for frequently occurring attacks. When such selection is carried out the yield from ambulatory EEG recordings may be even higher when compared to the basic, unfortunately no such studies

are currently found in the literature.

Several studies compare the ambulatory EEG with the clinical diagnosis. Callaghan and McCarthy (1982) for example, showed that 31% of patients, judged on clinical grounds to be suffering from epileptic attacks, proved to have non-epileptic attacks during ambulatory monitoring and 13% had mixed attacks. Conversely, of those judged to be suffering from syncope, 38% proved to have generalised or focal discharges in the ambulatory EEG. Overall, ambulatory monitoring gave additional information to the clinical opinion in 33% of patients and confirmed the diagnosis in a further 35%.

Berkovic et al. (1984) divided 87 patients into four groups depending on the effect of ambulatory monitoring on the clinical management. In 7% of cases the ambulatory EEG altered management because it suggested a different diagnosis. In 38% it provided support for the expected diagnosis. In 54% no additional information was gained and in 1% 'the data was not reconcilable with the clinical picture'. They note that continuation of monitoring after 48 hours was of value in only 4 of 19 patients.

Oxley et al. (1981) made an extensive study comparing findings during attacks recorded in the ambulatory EEG with; nursing staff's opinion of observed attacks, the psychiatric evaluation (without observation of attacks) and changes in prolactin levels. These authors found that the psychiatric opinion agreed with the EEG in 78% of cases

and prolactin levels were unhelpful except in patients with genuine tonic-clonic seizures. Extrapolation of their data also shows that the clinical opinion of the nursing staff agreed with the ambulatory EEG in 83% of cases. It should be emphasised however, that this was actually a control study to assess the validity of the technique in patients in whom there was no doubt about the diagnosis, there should therefore have been 100% agreement. It is interesting that when the ambulatory EEG was not in concordance with the other opinions it was assumed that a lack of EEG change during attacks was due to a timing error and not due to errors in clinical or psychiatric judgements.

In summary, ambulatory monitoring confirmed the suspected clinical opinion in an average of 35% of cases. Berkovic et al. (1984) found it changed the opinion in 7% whereas it added information to the clinical opinion in 33% of Callaghan and McCarthy's (1982) series. The results of Oxley et al. (1981) though valuable, cannot really be used in this assessment as this was a control study.

Perhaps the most appropriate method of evaluating ambulatory monitoring is to compare it to intensive in-patient monitoring although it should be remembered that in-patient monitoring is very expensive, disruptive to the patients' daily life and often reserved for a very select group of patients.

Ebersole and Bridgers (1985) compared EEG and video monitoring with ambulatory recording in the same patients. Reviewers

of one technique had no knowledge of the other investigation but had similar knowledge of referral details. Evidence for epilepsy was found in 18 of 25 referrals using intensive monitoring lasting from 1 to 11 days. Ambulatory monitoring, lasting for between 10 and 24 hours only, produced evidence for epilepsy in 15 of the 25 patients. However, intensive monitoring for the first day only, produced evidence for epilepsy in only 14 of 25 patients. This would therefore suggest that compared to one day of intensive in-patient monitoring, ambulatory monitoring provided almost the same amount of information. Longer periods of in-patient recording produced only 1.2 times the amount of information gained from a single 24 hour ambulatory EEG. There would therefore appear to be little difference between the two techniques particularly when one considers that ambulatory recording was carried out using 4 channels and intensive monitoring using 8 or 16.

A further study by Stores (1985) compares 8 channel cassette EEG recording to combined EEG and video monitoring in different patient populations. All recordings were made on children.

Useful results were obtained in 73% of patients using EEG with video recording and in 70% using ambulatory recording. It is possible therefore that ambulatory monitoring is not handicapped to any great degree by the inability to observe attacks directly. Furthermore, as Stores (1985) points out, "for EEG services outside special centres, cassette monitoring may offer greater scope than video in terms of range of

application and acceptance by children".

Finally, Ives and Woods (1979) evaluated the use of 4 channel ambulatory recording in patients with partial seizures as a 'first look' at seizure discharges prior to treatment. Eleven patients experienced partial seizures during 4 channel ambulatory recording and also during 16 channel cable telemetry with video monitoring. In all cases it was only possible to use ambulatory recording as a method of lateralising discharges and not for localisation. Several other patients experienced attacks during ambulatory recording only, abnormalities found during attacks were therefore compared to inter-ictal abnormalities found during cable telemetry. Results agreed in 22 of 24 patients and in one discordant record the ambulatory EEG results were later proven to be correct.

In summary, it would appear that ambulatory monitoring can provide additional information to the clinical opinion and also to the basic EEG. Studies have also shown that ambulatory monitoring can be equally as valuable as in-patient monitoring and can even provide an adequate guide to the lateralisation of discharges in patients with partial seizures. The study by Oxley et al. (1981) proves the validity of the technique using patients with unquestionable clinical pictures.

Reliability of ambulatory recording

The reliability of ambulatory recording apart from

technical difficulties, is solely dependent upon the reviewer. To date no studies have come to light which assess inter-laboratory concordance although this would be an interesting exercise.

Ebersole and Leroy (1983) did however investigate the degree of agreement between two reviewers from the same centre on 40, 3 channel ambulatory EEG recordings. The conclusions of the two reviewers were compared to the results of 8 channel cable telemetry. Seventeen of these patients underwent simultaneous ambulatory and cable telemetry EEG recording.

There was an overall concordance between both reviewers and cable telemetry in 77% of cases. When only simultaneous recordings were examined there was concordance in 96% of cases. The inter-reviewer reliability was 83% when tapes both with and without attacks were examined. In the 7 patients who experienced attacks, all tapes were correctly interpreted by both reviewers. One reviewer however, mistakenly diagnosed an artefactual event as ictal.

Leroy and Ebersole also illustrate the problem of interpretations of inter-ictal abnormalities. They found in fact, that non-epileptiform abnormalities such as 'slowing or scattered sharp activity' were commonly a source of disagreement both between reviewers and between the reviewer and the telemetered EEG. Fortunately, as they point out, often these types of abnormality are present and more easily interpreted during basic EEG recording.

There has been little work carried out therefore, assessing the reliability of ambulatory recording but to date results appear to suggest that the interpretation of ictal events may be a source of greater reliability than the interpretation of inter-ictal events. This leads to the inevitable question of how reliable are interpretations of basic EEG recordings?

Woody (1966) cited in Kiloh, McComas and Osselton (1972) gave the same 30 basic EEGs to one interpreter with a 6 month interval between reports. The measurement of the frequency of the alpha rhythm and its responsiveness was consistent, but measurements of other frequencies and the general assessment of the normality of the record were not significantly related.

Woody (1968) cited in Kiloh et al. (1972) also gave 30 records to three different reviewers and found that classification of records into 'normal or borderline and abnormal' showed agreement between 2 assessors in between 60 and 80% of cases. There was agreement between all three in only 53% of cases suggesting that the reliability of basic EEG reporting has its problems.

Ictal patterns of partial seizures

The diagnosis of partial seizures can be particularly difficult because the manifestations of attacks are so diverse. In terms of referrals for ambulatory monitoring it is frequently the case that the diagnosis is a choice between partial seizures and non-epileptic attacks. Unfortunately, the EEG changes found during partial seizures are not as widespread or as clearly differentiated as those during generalised seizures. As will be discussed later, many simple partial seizures (ie. attacks without impairment of consciousness) show no EEG changes at the scalp. It is extremely important therefore, for the ambulatory EEG reviewer to be aware of the symptomatology of simple and complex partial seizures (attacks with impairment of consciousness) so that negative EEG findings can be appropriately interpreted.

Patients with partial seizures comprise about 25% of all epilepsy referrals (Currie, Heathfield, Henson and Scott 1971). For 40-50% of patients the simple partial seizure is the first manifestation of an attack (the aura) and in some cases the only manifestation (Escueta and Walsh 1983). King and Ajmone Marsan (1977) found that 56% of patients experienced more than one type of aura.

The 1981 seizure classification includes simple partial seizures with motor, somatosensory or special sensory,

autonomic or psychic phenomena.

The simplest type of motor seizures are those with clonus, ie. contraction or relaxation of specific muscle groups (Browne and Erba 1983). These may extend to become the classical Jacksonian march which represents the spread of seizure activity along areas of the motor cortex located in the precentral gyrus. The attack begins with a sensation in the hand followed by tonic contraction of the thumb and fingers. Motor signs then spread to the muscles of the limbs and face; if the attack eventually becomes generalised consciousness is lost (Daly 1975).

Motor phenomena consisting of versive or postural changes may be seen in both simple and complex partial seizures and were found by King and Ajmone Marsan to be present in 80% of patients. Such motor phenomena may however, reflect the spread of discharges and not the cortical epileptogenic localisation (Escueta and Walsh 1983).

Although a cry may be heard at the onset of a tonic clonic seizure and mumbling may occur in some absence seizures, coherent phrases are characteristic only of partial seizures. Such phrases are distinct from warning cries such as "here it comes" when patients recognise an aura (Feldman 1983).

Speech arrest may also occur during attacks, usually beginning with numbness in the mouth area but with

preservation of understanding. Currie et al. (1971) noted speech disorders in 22% of patients, but usually as part of complex partial attacks.

Somatosensory or special sensory symptoms are more common components of simple partial seizures. Attacks usually consist of numbness or tingling in the whole or part of the body or an inability to move. King and Ajmone-Marsan (1977) found that visual hallucinations were as common as somatosensory symptoms. Desai (1984) claims that auditory hallucinations are rare in epilepsy and common in psychosis, Currie et al. (1971) however, found visual hallucinations in 18% of patients and auditory in 16%.

Daly (1975) suggest that complex visual scenes are rare in occurrence and do not necessarily represent past memories. The focus in this case is in the temporal lobe and not the primary visual cortex.

Olfactory and gustatory phenomena are less common than somatosensory and suggest a focus in the uncus or hippocampal gyri (Escueta and Walsh 1983). Symptoms commonly consist of the basic sensations of taste, eg. acid, bitter, salty, metallic. Most olfactory hallucinations are pleasant or unpleasant odours which the patient is unable to recognise (Currie et al. 1971).

Illusions are even less common, the patient may experience macropsia or micropsia, limbs feel detached, there may be

an increased sense of smell or hearing but gustatory illusions are rare (Daly 1975).

Vertiginous symptoms were found in 22% of patients by Currie et al. (1971) and were therefore more common than somatosensory sensations. These may include a feeling of dizziness or rotation (Daly 1975).

The most prevalent type of autonomic symptom in simple partial seizures is the epigastric aura. Blushing, salivation and pilo-erection may also occur. Incontinence is said to occur in about 15% of patients without loss of consciousness (Currie et al. 1971).

It is difficult to ascertain whether psychic symptoms are manifestations of simple or complex partial seizures although the 1981 classification suggests they are more commonly associated with complex partial seizures. The patient is often aware of the symptom but unable to control it. Symptoms may be mistaken for psychiatric disturbances although unlike these, they are brief and often accompanied by somatosensory symptoms. Such attacks occur in about 25% of patients (Lennox 1951).

Desai (1984) suggests that fear is the most common symptom, sometimes there is a fear of dying. King and Ajmone-Marsan (1977) however, found a feeling of strangeness or unreality to be as common as fear. They found *déjà vu* to be equally as common as fear but there were no

patients with jamais vu. Other emotions are; happiness (eg. the Russian author Dostoiewski), sadness and depression. Unpleasant emotions were found in 19% of patients by Currie et al. (1971). Sexual feelings and anger were found rarely as part of a seizure by Daly (1975).

When partial seizures are accompanied by an inability to carry out simple commands or willed movements and there is no contact with, or recollection of events, they are known as complex partial seizures. Attacks may be characterised by loss of awareness only or by loss of awareness and automatisms (Feldman 1983).

The 1981 classification of seizures defines automatisms as "more or less co-ordinated adapted (eupractic or dyspractic) involuntary motor activity". This may be, a continuation of activity already begun, a new activity initiated as consciousness is lost, an activity provoked by the patient's environment or provoked by other sensory components of the attack, eg. a gustatory sensation giving rise to chewing.

All of the features present during simple partial seizures may occur during complex partial seizures. The course of the attack may begin with a simple partial seizure followed by a complex partial seizure or the attack may be characterised by loss of awareness from the onset. Either of the above may become secondarily generalised ie. evolve into a tonic-clonic seizure.

Escueta, Kunze, Waddell, Boxley and Nadel (1977) observed two characteristic clinical types of complex partial seizures. Type I attacks consisted of an initial blank stare lasting around 10 seconds during which the patient did not respond to voice or pain. This was followed by a second phase of stereotyped movements, eg. chewing, blinking and swallowing lasting for between 10 and 60 seconds. The final phase of the attack consisted of reactive automatisms during which the patient would respond to external stimuli with co-ordinated motor activity. During this final phase consciousness was still clouded but some patients would respond to verbal stimuli and pain.

Type II attacks consisted of reactive automatisms and clouding of consciousness or clouding of consciousness only. These kind of attacks were less common than type I.

The automatisms seen during complex partial seizures tend to be more sophisticated than those seen during absence seizures and the attacks themselves tend to be longer than absences which characteristically last for up to 15 seconds (Escueta and Walsh 1983).

Automatisms can be divided into 5 categories (Gastaut and Broughton 1972). Alimentary automatisms consisting of swallowing, salivating, chewing and sucking were found by Escueta and Walsh (1983) to be the most common. Mimetic automatisms include facial expressions consistent with

fear, bewilderment, discomfort, tranquility, laughing (gelastic seizures) or crying. Gestural automatisms including repetitive movements of the hands, the acting out of seemingly complex tasks and sexual gestures such as pelvic thrusting and masturbation. Ambulatory automatisms, including running or walking were found to be infrequent and occurred only in type II attacks according to Escueta and Walsh (1983).

In order to assess the severity of attacks recorded during ambulatory monitoring, it is advisable to question both patient and observers about the presence or absence of post-ictal symptoms. It has been suggested that brief partial seizures are not accompanied by post-ictal symptoms. Escueta and Walsh (1983) however, have found that after partial seizures consciousness returned slowly unlike the immediate recovery of patients with absence seizures. Escueta et al. (1977) found confusion persisting after attacks in 18 of 21 patients whilst Dinner, Luders, Rother and Erenberg (1984) found post-ictal lethargy or sleep in 19 of 30 patients but confusion in only 7. Todd's paresis was found in only 7 of 199 of King and Ajmone-Marsan's (1977) patients. A nominal dysphasia was found in 31 of 83 patients tested, especially those with left temporal foci and 7 of 199 patients were combative whilst being restrained in the post-ictal period (King and Ajmone Marsan 1977).

During attacks Escueta et al. (1977) tested responses to



pinprick, deep pain, touch and corneal reflexes. During the initial phase of attacks no patient showed any response but when reactive automatisms appeared towards the end of attacks, some patients responded to verbal and painful stimuli.

Unusual precipitants of attacks have been said to occur mainly in pseudoseizures. However, Reader and Wright (1982) report a simple partial seizure manifesting as tonic straightening in the right arm which was evoked by eating. Other precipitants of reflex epilepsy which have been reported are; touch, movement, proprioception, autonomic stimuli and reading and writing. In some patients a strong sensory input may avert attacks (Reader and Wright 1982). Stress has also been shown by Currie et al. (1971) to precipitate attacks in 21% of patients.

It has also been suggested that genuine seizures are stereotyped whereas pseudoseizures are not. Schmidt, Machus, Porter and Penry (1982) however, showed that when 2 complex partial seizures were examined in 9 patients between 41 and 71% of ictal signs were common to both attacks. When 8 seizures were examined in one patient only 33% of signs were common to all attacks. Thus even genuine partial seizures may show great intra individual variability.

Diagnosis of partial seizures

In 75% of patients with partial seizures the onset occurs

before 20 years of age (Desai 1984). King and Ajmone Marsan (1977) found 14 years to be the mean age of onset, whereas Currie et al. (1971) found this to be 28 years. Such differences may reflect the fact that King and Ajmone Marsan's patients were surgical candidates implying severe cases whereas Currie et al.'s. were a large unselected population.

There is very little evidence for a genetic predisposition in partial seizures (Feldman 1983; Giurgiuca 1984). However, King and Ajmone Marsan (1977) and Currie et al. (1971) found a history of epilepsy in relatives in 18 and 11% of patients respectively.

It is possible that a history of febrile convulsions may play a role in the pathogenesis of partial seizures. Between 5 and 30% of patients may have such a history (Dinner et al. 1984; Currie et al. 1971). This is higher than the 2.4% found in the normal population (Ross and Peckham 1983). The number of patients who experience secondarily generalised tonic clonic seizures ranges from 37% (Dinner et al. 1984) to 71% (Escueta et al. 1977).

The aetiology of partial seizures is determinable in 28% of cases (Hauser and Kurland 1975; cited in Penry 1975). Findings may however be biased because they are often based on severe intractable cases or surgical candidates. CT scans were abnormal in 38% of cases according to Feldman (1983) and King and Ajmone Marsan (1977). Tumours

have been found to be present in between 1% (Giurgiuca 1984) and 10% (Currie et al. 1971) of patients. Mesial temporal sclerosis was found in almost half of surgical candidates by Penry (1975).

Head trauma was cited as a possible aetiology in 4% of cases by Dinner et al. (1984) and 22% by King and Ajmone Marsan (1977). These differences may be due to the definition of significant head trauma. Abnormal births were present in 7% of patients seen by Currie et al. (1971) and 14% seen by King and Ajmone Marsan (1977) and Giurgiuca (1984).

Many patients referred for ambulatory EEG monitoring with a diagnosis of non-epileptic attacks or partial seizures are referred by psychiatrists. Although a controversial area, it has been suggested that there is an increased incidence of psychiatric disturbances in patients with inter-ictal left anterior temporal foci (Giurgiuca 1984). Compared to a control group of patients with generalised tonic clonic seizures, Shukla, Srivastava, Katiyar, Joshi and Mohan (1979) found a higher incidence of early emotional disturbances, neuroses, schizophrenia and behaviour disorder in patients with partial seizures.

After an extensive review of the literature however, Stevens (1975) concludes that persons with psychiatric disturbances, but not epilepsy, may show more temporal EEG abnormalities than normal. However, few patients with

partial seizures actually develop psychiatric disturbances.

The EEG in partial seizures

Klass (1975) discusses the inter-ictal EEG abnormalities which are found in patients with partial seizures. He states that different types of attacks occur in patients with the same inter-ictal EEG abnormalities and that the abnormality may itself vary depending on the patient's level of arousal. He notes that approximately 25-33% of patients have bilateral temporal lobe abnormalities which may be independent, synchronous or transmitted from one temporal lobe to another. He notes that in adults EEG abnormalities commonly occur in anterior temporal regions whereas in children foci may appear more often in mid-temporal and sylvian regions.

In some patients a precursor may appear in the frontal lobe which triggers a generalised burst of spike and wave. Citing Gabor and Ajmone-Marsan (1969), Klass points out that patients with focal abnormalities in the EEG are more likely to have partial seizures than patients with diffuse paroxysmal discharges (55% compared to 24%). When both types of abnormality are seen in the EEG there is an increased frequency of secondarily generalised seizures.

Abnormality tends to consist of spikes and sharp waves or localised slowing. Klass states that when extra electrodes are applied and activation procedures used

the proportion of patients with a normal inter-ictal EEG is around 10% or less.

Currie et al. (1971) reviewed 660 patients with partial seizures and found that taking into account up to 3 EEGs on each patient, 92% had definite focal abnormalities, 6% had an ill-defined focus and only 2% no focus. Thirty percent of abnormalities consisted of sharp waves or spikes, 40% were slow waves and 30% were mixed. Of these patients, 297 had sleep recordings and definite abnormalities were found in 98%. In 52% of patients there was a left sided focus, 29% were right sided and 19% were bilateral.

Klass (1975) describes the EEG pattern found during partial seizures as similar to that found by Gibbs and Gibbs (1982) "a gradual transition, during which spikes become increasingly more frequent and, in conjunction with rhythmic theta activity, assume the appearance of a sustained rhythm". Other authors, he states, have noted focal or diffuse suppression of normal rhythms at the onset of seizures which originate deep in the temporal and mesial frontal regions. He notes that there is general agreement that abnormalities are widespread when there is loss of consciousness and automatisms. Gastaut, Nanquet, Vigouroux, Roger and Badier (1983) found Gibb's pattern in 46% of cases, rhythmic waves in the temporal region in 18% and generalised 14-20cps activity in 7%. In a further 29% there was no EEG change although Klass does not state what types of partial seizures these were.

Conversely, he states that Klass, Espinosa and Fischer-Williams (1973) found that only 3% of attacks showed no EEG change throughout the entire episode.

Studies comparing the EEG recorded from the scalp, the surface of the cortex and also from deeper structures have been carried out in patients with intractable partial seizures who were being investigated for surgery. Lieb, Walsh, Babb, Walter and Crandall (1976) found that 86% of clinically observable seizures (ie. with automatisms or loss of awareness) were accompanied by an EEG change at electrodes implanted in the skull. Only 19% of seizures consisting of an aura alone however, showed changes at the skull. Depth recordings were made from the hippocampal pes, hippocampal gyrus, the amygdalla and occasionally from the thalamus and uncus. Surface recordings were made from standard 10-20 positions. The authors note however, that recording channels were biased towards depth electrodes and in some cases the surface temporal derivations were not included. More extensive recordings might therefore produce further surface EEG changes.

It was also shown that the initial changes in the surface EEG occurred ipsilaterally or bilaterally but never contralaterally to the depth location. However, ipsilateral changes were found on the surface in some patients when depth channels showed bilateral involvement. They also found some variation between attacks in the same patient and recommend the recording of several seizures.

Surface EEG changes were less well defined with a loss of high frequency activity due to the distance of the EEG from the deeper source.

In a similar study, Escueta and Walsh (1983) note that "current information does not substantiate previous assertions that scalp and nasopharyngeal and sphenoidal electrodes have false localising properties". They note that when the clinical symptom preceded the appearance of focal EEG changes the actual focus was situated at some distance from the scalp electrodes. In several attacks in one patient they noted only a desynchrony in the surface EEG on the same side as the depth changes.

Goldensohn (1983) suggests that spiking seen on scalp recordings arises from discharges involving several square centimetres of the cortex. Citing Penfield and Jasper (1954) he states that the area of the cortex involved in producing recognisable scalp EEG changes would have to be approximately 3cm^2 . He further illustrates that a single focus may be apparent from conventional scalp recording positions but electrodes spaced closely together on the cortex will show independent foci within an area of a few millimetres indicating several epileptogenic zones. Goldensohn (1975) states that between 20 and 70% of spikes present on the cortex are not seen on the scalp. Although there is great variability recordings from the scalp may be attenuated by about 70%. Escueta, Kunze, Waddell, Boxley and Nadel (1977) investigated the types of EEG chang

associated with different phases of partial seizures. Seizures beginning with an initial stare and loss of awareness showed focal or lateralised low voltage fast activity at 18-30cps or 10-12cps followed by slower, higher amplitude focal or lateralised sharp waves as de novo stereotyped automatisms appeared. As the attack progressed to reactive automatisms with clouding of consciousness, the EEG changes became characterised by more diffuse slowing. Changes appeared earlier, and were of greater amplitude and preponderance in nasopharyngeal electrodes compared to scalp electrodes.

Patients who experienced initial reactive automatisms and clouding of awareness but no initial staring and de novo automatisms showed minimal diffuse slowing only, at around 6cps. Escueta et al.(1977) found that in 7 of 14 patients EEG rhythms returned to normal whilst the patient was still confused.

Ambulatory monitoring in the diagnosis of partial seizures

The limited number of EEG channels available for ambulatory recording precludes the possibility of its use as a method of accurately localising partial seizures. It is therefore not a substitute for the intensive monitoring carried out on surgical candidates which also requires depth recording although Ives and Woods (1979) have used sphenoidal electrodes during 4 channel recording. These authors argue

however, that once localisation has been ascertained on the basis of the inter-ictal EEG and clinical grounds, the ambulatory EEG can provide a 'first look' at seizures during the work up to surgery.

Ives and Woods (1979) studied 100 patients of which 82 experienced 371 clinical or electrographical events. The average age of patients was 24 years and there were equal numbers of males and females. Of the recorded attacks, 14% consisted of simple partial seizures, 55% were clinically observed partial seizures and 31% were electrographic seizures without observed clinical accompaniment. Twenty one percent of clinical events however, showed no EEG change and 58% of these were auras. In fact in only 5 (10%) of the attacks which consisted of auras alone, did an EEG change occur. These findings are therefore consistent with those of Lieb et al. (1976). Of the clinically observable attacks, 16% went undetected by the scalp EEG.

Ives and Woods then went on to examine unilateral attacks only, in further detail. These comprised 50% of recorded events. Thirteen patients showed left sided lateralisation and 11 right sided lateralisation. In 11 patients with documented seizures on both ambulatory EEG and 16 channel telemetry or basic EEG recording, the lateralisation was consistent. As discussed earlier, attacks during ambulatory EEG recording were not reconcilable with other inter-ictal recordings in only one of the remaining 13 patients.

Ives and Woods therefore conclude that once localisation has been made to the temporal lobes, 4 channel ambulatory recording is capable of lateralising attacks and is useful because spontaneous seizures are more likely to be recorded than during the basic EEG. The exact focus of the EEG discharge cannot however, be ascertained without the back up of other more elaborate systems.

The only other report concerning the use of 4 channel recording in surgical candidates is that of Ramsay (1981). Recording was carried out in 5 patients during the work up to lobectomy and in all 5 cases lateralisation was the same as that seen in routine and depth recordings.

Remaining reports which seek to elucidate the type of seizure when there is no doubt about the diagnosis of epilepsy, are anecdotal. In these patients recording is usually carried out in order to determine the choice of anticonvulsant. It is stated however by Blumhardt (1986), that some authors possibly group such patients with those in whom the diagnosis is in doubt. This then increases the number of patients in whom epilepsy is confirmed. The following authors do however differentiate the two groups.

Declerk et al. (1982) note that in 74% of 31 patients a better description of the type of attack was obtained. Zschocke et al. (1982) found long runs of spike and wave activity lasting between 16 and 42 minutes in one 41 year old patient who suffered periods of disorientation. He

had understandably, been diagnosed as having complex partial seizures. Berkovic et al. (1984) likewise found they were able to change a diagnosis of partial seizures in two patients to absences and tonic seizures. Conversely one patient thought to have generalised epilepsy showed focal discharges during a seizure.

Reports of 8 channel recordings are as yet few. Ebersole and Bridgers (1985) did illustrate however, that complex partial seizures were equally detectable on simultaneous 3 and 8 channel ambulatory EEG recording in 7 patients. Bridgers and Ebersole (1985) also note that in 2 patients referred for classification of seizures, 3 channel ambulatory EEG recording and 8 channel cable telemetry were equally as effective. Finally, Stores (1986) found that attacks recorded on the 8 channel ambulatory EEG provided additional information in 20 of 23 patients with known seizure disorders in whom the sleep and basic EEG were equivocal.

One final aspect of the recording of partial seizures perhaps should be mentioned. Blumhardt and Oozeer (1981) found that in patients with partial seizures which become secondarily generalised the ECG showed tachycardia of abrupt onset at the time of the EEG change. Preceding the seizure, on some occasions, they observed a brief period of slowing in heart rate. Towards the end of the EEG discharge they noted rate changes, sinus arrest and extrasystoles. In most non-epileptic attacks they found

sinus tachycardia beginning well before clinical symptoms. These findings serve to illustrate that ECG changes during attacks should be treated with caution, particularly in light of the possibility that some partial seizures may show no scalp EEG changes (Lieb 1976; Ives and Woods 1979).

In 1986, Blumhardt, Smith and Owen enlarged on these findings with 76 complex partial seizures recorded from 26 patients. EEG recording was made from the mid temporal to parietal positions T4 P4 and T3 P3.

In 30% of attacks the heart rate exceeded 140 beats per minute (bpm). In 12% it exceeded 160bpm and in 4% it exceeded 190bpm. In 70% of patients the changes were less marked.

In one third of attacks there was an initial slowing prior to the tachycardia. Towards the end of the attack the tachycardia was followed by bouts of irregular accelerating and decelerating. In one patient there was "considerable bradycardia".

Unlike their earlier report, Blumhardt et al. found that the ECG acceleration preceded the EEG change by an average of 10 seconds. It is stated that this may be due to lack of scalp coverage or lack of scalp EEG changes. They note that Marshall, Westmoreland and Sharborough (1983) found sinus tachycardia after the onset of seizure discharges in a similar group of patients using multi-channel recording.

Blumhardt et al's. findings may also be due to their electrode positioning. Leroy and Ebersole (1983), as mentioned earlier, showed that anteriorly biased montages were more likely to record abnormality in patients with partial seizures.

Blumhardt et al. also suggest that these cardiac changes could aid in the diagnosis of attacks during which the EEG is obscured by muscle activity or there is a lack of scalp EEG changes. Until the ECG changes associated with non-epileptic attacks are well documented, this suggestion should be treated with extreme caution especially in light of Blumhardt and Oozeer's 1981 findings.

Thus, it would appear that changes in heart rate can occur during both genuine and non-epileptic seizures.

When there is insufficient scalp EEG coverage, ECG findings must be interpreted with caution as the EEG change may not be obvious.

Introduction

During most generalised seizures EEG changes are widespread and easily differentiated. Three channel ambulatory recording is therefore an adequate method of recording. When patients are referred for the quantification of attacks such as absence seizures, 8 channel recording is unnecessary. It is therefore important to have an adequate knowledge of the ictal patterns of generalised seizures so that the appropriate method of recording can be chosen. When attacks are possibly secondarily generalised however, 8 channel recording is required.

Ictal patterns of absence seizures

A most extensive study of absence seizures was carried out by Penry, Porter and Dreifuss (1975). They examined 374 attacks in 48 patients and distinguished two different types of attacks and 5 components of attacks.

Simple absences (according to the 1981 Classification) now known as absences with impairment of consciousness only), are characterised by a sudden vacant stare and cessation of any ongoing activity. The patient is largely unresponsive although some may grunt in reply to questions. The attack ends suddenly and the patient resumes his pre-ictal activity although he may have

lost the train of conversation. Only 9% of patients studied by Penry et al. (1975) had this as one type of attack. Without help from the background EEG this type of attack could be misdiagnosed as a partial seizure with impairment of consciousness only. These attacks are however, quite rare and are estimated by Caffi (1973) (cited by Penry et al.) to occur in less than 5% of patients.

The second type of absence seizure is said to be accompanied by additional components. Firstly, mild clonic components such as eyelid flicker, finger, arm or shoulder twitching or even a generalised myoclonic jerk which will cause the patient to drop something. This was seen in 46% of attacks. Secondly, increased postural tone which may manifest itself as back arching, stretching of the head backwards or if standing a backward fall was present in 5% of attacks. Thirdly, atonic components which may lead to dropping of the head or slumping, knees buckling if standing but rarely to falling, were seen in 23% of attacks. Fourthly, Penry et al. describe autonomic phenomena such as pupil dilation, pallor, flushing, pilo-erection, tachycardia, salivation and occasionally incontinence. Autonomic symptoms may however, be difficult to discern. Finally, they describe absences with automatisms. These were observed in 63% of attacks and in most cases consisted of movements of the face or head especially lip smacking, chewing, swallowing and yawning. In 15% of attacks there was fumbling with the fingers. They found

that 50% of attacks lasting longer than 7 seconds showed automatisms and 95% of those lasting longer than 18 seconds showed automatisms.

Many attacks were accompanied by more than one of the above components, the most often occurring being mild clonic components and automatisms or decreased postural tone and automatisms.

Twenty nine percent of attacks were spontaneous, 53% were evoked by hyperventilation and 18% were evoked by photic stimulation (38% of these showed eyelid myoclonia).

In the differentiation of partial seizures and absence seizures Penry et al. suggest that it is important to note that most absence seizures last 10 seconds or less and rarely continue for longer than 45 seconds.

The EEG in absence seizures

Many authors (Fenwick 1983; Luders, Lesser, Dinner and Morris 1984; Browne and Mirsky 1983) now accept that subcortical structures play a secondary role in the production of generalised spike and wave activity. Gloor (1979) has proposed on the basis of work with cats, that the cortex has a hyper-excitable state which reacts abnormally to "afferent thalamocortical volleys normally involved in the elicitation of spindles". This hyper-excitability may be due to a genetically determined biochemical aberration mediated through a gene with variable

penetrance at different ages (Fenwick 1983).

Browne and Mirsky (1983) reiterate that spikes originate from excitatory post-synaptic potentials (EPSPs) and slow waves from inhibitory post synaptic potentials (IPSPs). The slow wave itself represents the IPSP reacting to volleys of EPSPs and they argue that absences are largely characterised by inhibitory phenomena. Some evidence suggests that drugs which are effective in absence seizures restrict inhibitory pathways whereas those that are used primarily for partial seizures do not.

As Fenwick (1983) has pointed out, perfectly symmetrical and synchronous spike and wave activity over the whole of the scalp is rarely seen. Other work has shown that spikes and waves travel at different rates over the cortex.

According to the 1981 seizure classification, all clinical absence seizures are accompanied by bilateral 2-4 c.p.s. spike or polyspike and wave activity. According to Erba and Browne (1983) the spike is sharp and of the same amplitude as the wave which is smooth and regular. Discharges are often provoked by hyperventilation, sleep and sometimes by photic stimulation. The inter-ictal EEG is usually normal but may show occasional paroxysms of spike and wave.

This form of spike and wave contrasts to that seen during atypical absence seizures in which the spikes may be

blunted or missing and of higher amplitude than the wave which is irregular and slower at around 1-2 c.p.s. This type of discharge is rarely precipitated by hyperventilation and photic stimulation but often provoked by sleep. The inter-ictal EEG shows paroxysms of spike and wave and in the cases in which attacks are symptomatic of an underlying encephalopathy there may also be slowing of the background EEG.

Dondey (1983) examined the topographical distribution of spike and wave paroxysms in 46 patients using transverse arrays of electrodes. He found one group of patients with two symmetrical maxima at lateral electrodes placed 7.5cm. from the midline. These patients showed mainly absences with little clinical signs and 3-3.5 c.p.s. spike and wave. In all but one patient the outcome was favourable and only one had tonic clonic seizures.

He also identified a second group of patients with a single maximum point in the midline. All but one of these patients showed an increase in muscular tone, myoclonus or automatisms and most had spike and wave faster or slower than 3 c.p.s. In most patients the outcome was not favourable and most also had other forms of seizures. The author concludes that this kind of differentiation is "of better prognostic value than the classical one, which opposes typical to atypical discharges".

Diagnosis of absence seizures

Livingston, Torres, Pauli and Rider (1965) found that of 15,102 patients with epilepsy only 2.3% had "true petit mal". In another large study, Gastaut, Gastaut, Silva and Sanchez (1975) found that 18% of children with epilepsy under the age of 15 years had absences, whereas only 3% of patients older than 15 years had absences. The overall incidence was 10%. Gastaut (1982) states that absences may be more common in females.

The age of onset of absence seizures has been found to range from as early as 9 months by Sato, Dreifuss, Penry, Kirby and Palesch (1983) to 15 years by most authors (Livingston et al. 1965; Brown and Mirsky (1983). Livingston et al. found that attacks ceased in 77% of patients, and 96% of these ceased before the age of 20 years. Sato et al (1983) found similarly, that attacks ceased in 75% of patients who had absences only, but ceased in only 34% of those who had absences and tonic-clonic seizures.

There is little evidence of neurological abnormalities in patients with absence seizures. Sato, Dreifuss and Penry (1976) found mild abnormalities in 14% of patients with absence seizures only. Browne and Mirsky (1983) in a review of the literature estimate that between 0 and 10% of patients show CT scan abnormalities.

Livingston et al. (1965) found a history of febrile

convulsions in 3.4% of their patients whereas Penry, Porter and Dreifuss (1978) found this in 15%. Gastaut (1982) also states that a history of febrile convulsions is often encountered in patients with absences.

A family history of epilepsy seems to be prevalent in many patients with absences and gives weight to a genetic predisposition. Sato et al. (1983) found this in 48%. Browne and Mirsky (1983) citing Lennox and Lennox (1960) found that a family history was present in 34% of patients with 3 c.p.s. spike and wave. Monozygotic twins showed a 75% concordance for absence seizures and 84% for 3 c.p.s. spike and wave activity.

It has been suggested that automatisms during partial seizures are more complex than those seen during absences (Escueta and Walsh, 1983). Penry and Dreifuss (1969) however, argue against this. They found perseverative, de novo and reactive automatisms in many patients and suggest that the mechanism underlying automatisms is the same for both partial seizures and absence seizures. They note that a spread of the epileptic discharge is necessary for the occurrence of automatisms in partial seizures.

Ictal patterns of tonic-clonic seizures

Gastaut and Broughton (1972) give a detailed description of the tonic clonic seizure from which the following account is derived.

Attacks sometimes begin with a series of brief, bilateral and massive muscular contractions with an EEG accompaniment of generalised polyspike and wave activity. This is followed by a brief period of EEG attenuation for 1 to 2 seconds or there may be low voltage fast activity at 20 c.p.s. This activity may however, be masked by muscle artefact which marks the onset of the tonic phase of the attack.

Even if the pre-ictal myoclonus is absent the remaining features of attacks are stereotyped. The tonic phase consists of contraction of muscles of the trunk, face and neck, forcing the body forward, the eyelids to be drawn open and the eyes to roll upwards. The jaw muscles also contract and the mouth becomes rigid and half open. Next there is involvement of the shoulder muscles, the shoulders rise, the arms become elevated and finally the arms become semi-flexed and outwardly rotated. The legs may show similar changes to a lesser extent with flexion and outward rotation.

The tonic phase then becomes one of extension rather than flexion, the neck and back arch and the mouth opens wide and then snaps shut (sometimes causing tongue biting). The thoracic muscles contract forcing air out of the lungs and a cry lasting for between 2 and 12 seconds may be heard. The arms now cross in front of the chest but later become extended, wrists and fingers may also extend or the wrists extend and the fists clench. The legs may also show

extension as do the feet and big toes.

The tonic phase is characterised by an EEG pattern of surface negative waves at 10 c.p.s. which gradually increase in amplitude. This fast activity then becomes interrupted by occasional slow waves which become more and more abundant. The onset of slow waves marks the "vibratory" period of attacks.

During this phase there is a build-up of fine tremor beginning at about 8/sec and slowing to 4/sec. The EEG eventually shows 4 c.p.s. polyspikes and slow waves and the clonic phase of the attack begins.

Each slow wave is accompanied by a decrease in muscular tone which eventually becomes sufficient to completely interrupt the tonic phase causing violent myoclonic jerks throughout the entire body each associated with a burst of polyspikes in the EEG. The tongue may also be bitten at this stage and each jerk may be associated with a cry. The attack gradually ends with a final massive myoclonus.

From the beginning of the attack there are marked autonomic changes, the heart rate can double, the blood pressure rises and there is a six-fold increase in bladder pressure. The skin changes from pallor to flushing to cyanosis and there is pilo-erection. An increase in glandular secretions causes perspiration and increased salivation. At the point that air is expelled from the lungs during the tonic phase, respiration ceases and may

remain absent until the post-ictal phase. The pupils are dilated during the tonic phase and dilate and contract during the clonic phase.

After the final myoclonus the EEG flattens and the patient enters the post-ictal phase. For a very brief period some muscles become flaccid and urinary incontinence may occur (less frequently faecal incontinence). There is then further tonic contraction of some muscle groups particularly those of the face and jaw but less so the limbs. The eyes may still deviate and there is cardiac arrhythmia. Breathing returns through clenched teeth and frothy saliva appears. Slow waves in the delta range replace the flattening and the patient remains totally unresponsive with an absence of pupil response, deep tendon reflexes are exaggerated and there is no response to painful stimuli.

As the EEG moves from the delta range to the theta range the patient enters the recuperative phase, he may be confused or show reactive automatisms. Gradually all responses return to normal. Many patients actually go straight from the post-ictal coma into sleep. On awakening, patients often complain of headache and experience a retrograde amnesia.

Luders et al. (1984) suggest that the post-ictal phase represents neuronal exhaustion because the increased

neuronal and motor activity has consumed vast amounts of energy reserves. The interference with respiration has also restricted oxygen supply. They state though, that other factors such as inhibitory mechanism, must play a part in bringing attacks to an end because absence seizures cease without post-ictal clinical and EEG changes.

Masuhr (1979) analysed 10 video-recorded tonic-clonic seizures and found that the tonic phase characteristically lasted from 25 to 30 seconds and the clonic phase from 45 to 50 seconds. He also noted that in tonic-clonic seizures which are secondarily generalised the attack may last from 10 seconds to one minute longer than primary generalised tonic-clonic attacks.

Diagnosis of tonic-clonic seizures

Primary generalised tonic-clonic seizures occur in 11% of patients with epilepsy and secondary generalised tonic-clonic seizures occur in a further 12.5% of patients (Gastaut 1975). Gastaut (1982) notes that primary tonic-clonic seizures occur in childhood more frequently in males than females, 20% have a family history of epilepsy and a personal history of febrile convulsions and in 80% the outcome is favourable. Conversely, Browne (1982) estimates that only between 7 and 10% of patients' relatives have a history of non-febrile seizures. Gastaut (1981) notes that adolescence is a "golden age" for tonic-clonic seizures, many being precipitated by lack of sleep, fatigue and alcohol. Attacks occur more frequently just before

and after waking.

Only 20% of primary tonic-clonic seizures begin in adulthood and most cases of late onset occur in women of menopausal age who may also have had attacks during adolescence. In old age, Gastaut (1982) states that tonic-clonic seizures are very rare and are secondary to diffuse cortical atrophy and attacks occur mainly in males.

In a review of the literature, Browne (1982) suggests that animal studies show the onset of the tonic-clonic seizure to be in the midbrain reticular formation, after a few seconds the thalamus, cortex and limbic structure become involved. The hypersynchronous discharge in the reticular formation may possibly be due to a hereditary-genetic biochemical or structural abnormality although there is no clinical or EEG evidence of structural lesions in patients with primary tonic-clonic seizures.

Inter-ictal EEG in tonic-clonic seizures

Gastaut and Broughton (1972) found that patients with primary generalised tonic-clonic seizures usually had normal background EEGs or occasional generalised polyspike or spike and wave discharges. Quite frequently the spike and wave was at 4-5 c.p.s. especially in adults.

Other forms of generalised seizures

Atypical absence seizures, myoclonic, atonic and tonic

seizures are often observed in varying combinations as part of the Lennox-Gastaut syndrome. They have a poor prognosis and are associated with an encephalopathy, mental retardation and neurological problems (Erba and Brownel1983).

Occasionally, attacks occur in relation to other metabolic, infectious or degenerative problems and in this case are termed secondary generalised seizures. Only a minority of patients have these types of primary generalised seizure which are relatively benign.

Atypical absence seizures show similar components to absences but symptoms are more pronounced. The EEG accompaniment may consist of slow spike and wave activity, flattening, low voltage fast activity which increases in amplitude, 10 c.p.s. activity or any combination of the last three. Gastaut et al. (1974) (cited by Erba and Browne) state that during some attacks which show slow spike and wave activity, the onset and cessation of attacks may be more gradual and there may be decreased responsiveness rather than complete impairment of consciousness.

Myoclonic attacks include infantile spasms or salaam spasms which occur in most infants before the first year. The background EEG shows hypsarrhythmia and the EEG at the time of the attack shows low amplitude beta or alpha frequencies (Luderset al. 1984). Other myoclonic attacks include bilateral epileptic myoclonus during which there

are generalised jerks without loss of consciousness and the EEG shows polyspikes, polyspike and wave or slow spike and wave (Erba and Browne 1983).

Atonic or astatic seizures are characterised by sagging of the body, falling to the floor or nodding of the head, they often last for less than 4 seconds and there is no loss of consciousness or post-ictal confusion. The inter-ictal EEG shows, most commonly, slow spike and wave activity and the ictal record shows similar changes to those seen during atypical absence seizures (Erba and Browne 1983).

Chatrian, Lettich, Wilkins and Vallarta (1982) made an extensive study of tonic seizures in 35 patients. They recorded 116 attacks in 28 patients, 17 of which occurred during waking (3 provoked by overbreathing) and 99 during sleep. Attacks varied from minimal tonic contractions to intense spasms causing flexion of the entire body. Twenty patients experienced some arrest or alteration in respiration, in 2 patients whose attacks occurred during wakefulness, unresponsiveness was demonstrated during the attack but there was no post-ictal confusion.

The EEG during attacks showed most commonly, high voltage 15-20 c.p.s. activity occurring bilaterally. The frequency of the discharge often decreased as the attack progressed but the voltage sometimes waxed and waned. In a few patients attacks were preceded by low voltage fast activity or spike and wave paroxysms. The post-ictal EEG was characterised by high voltage widespread delta waves,

spike and slow waves or sharp and slow waves. In 6 patients there was a prompt return to the pre-ictal pattern. During the post-ictal EEG phase some patients showed lip smacking, chewing or swallowing automatisms.

The inter-ictal EEGs in these patients commonly showed widespread slow atypical spike and wave discharges or focal or lateralised spiking and widespread alterations in background rhythms.

Ambulatory monitoring in the diagnosis and treatment of generalised seizures

Few reported cases of primary tonic-clonic seizures are found in the literature on ambulatory EEG recording. The reason for this is uncertain, possibly it arises from the fact that tonic-clonic seizures are so easily diagnosed from the classical description of symptoms. Such patients may therefore rarely be referred for ambulatory recording. In some cases it is unclear whether recorded attacks were absences or tonic-clonic seizures as it is often simply stated that a certain number of generalised seizures were recorded, eg. Ebersole and Bridgers (1985), Declerck et al. (1982).

In their validity study, Oxley et al. (1981) recorded tonic-clonic seizures in 4 cases using 4 channel recording. They found that the EEG showed movement artefact during attacks followed by post-ictal slowing. They also found that in contrast to pseudoseizures and partial attacks,

prolactin levels were raised after the attack. They also recorded one "tonic-atonic" seizure and one "tonic semi-purposeful attack", both were accompanied by paroxysmal slow waves.

The value of ambulatory recording in patients with tonic attacks has been highlighted by Berkovic et al. (1984). One patient thought to be suffering from partial seizures experienced a tonic attack and the diagnosis was changed to Lennox-Gastaut syndrome. In 5 patients, tonic-clonic seizures were recorded, in 2 absences and in 5 tonic seizures, thus supporting the previously suspected diagnosis. Berkovic et al. note that tonic seizures may be very brief and are more frequent at night. In fact in a number of patients there was "subclinical status epilepticus" during sleep. The EEG pattern during attacks was one of a "generalised electrodecremental response followed by rapid epileptic recruiting rhythm". This EEG pattern produced a characteristic rumble on the replay deck which often made audio detection easier than visual. In at least one patient, attacks occurred well after the first hour of sleep, so the only substitute for ambulatory EEG recording would have been an all-night laboratory recording.

Ambulatory recording has also shown its value in differentiating between primary and secondarily generalised seizures although in these instances 8 channel recording may be the most efficient. Stores (1985) illustrates such a case in a 7 year old girl. Four channel ambulatory EEG recording showed both generalised spike and wave discharges

and also multifocal slow and sharp waves of unclear significance. An 8 channel recording however, showed a consistent focal discharge in the left posterior quadrant immediately preceding the generalised bursts.

Absence seizures are said, in the majority of cases, to be provoked by hyperventilation during basic EEG recording (Penry et al. 1975). However, there are several reports in the literature citing instances of normal basic EEGs in patients who showed absences during ambulatory recordings. In one 32 year old patient studied by Ives et al. (1981) absence seizures had not been experienced for 8 years and the basic EEG was normal. He suddenly developed episodes of loss of memory and face and arm twitching, on ambulatory recording these attacks proved to be accompanied by 3 c.p.s. spike and wave activity.

Stores (1985) cites a similar case. An 11 year old boy with a past history of seizures began to suffer from poor school performance. A standard EEG and even a sleep deprived and sleep EEG showed nothing significant. Seventy-four hours of ambulatory EEG recording however, showed frequent generalised spike and wave discharges including episodes of status for up to 12.5 minutes. Attacks were accompanied by clouding of consciousness which was obvious only on close scrutiny.

Several authors have used ambulatory monitoring to assess the effect of the environment on spike and wave discharges in children with absences. This in fact, is one of the

advantages of ambulatory monitoring and there is no other comparable technique by which to record patients in their own environment. As abnormality is generalised, 3 channel recording is perfectly adequate.

Davidson et al. (1981) recorded 3 patients in order to assess whether subclinical paroxysms were contributing to problems at school. Two patients, one of whom was photosensitive, showed no discharges but one showed frequent polyspike and slow wave discharges. Another patient noted during recording that at times she felt unwell and mentally slow. No obvious attacks occurred but the EEG revealed that during these periods there were frequent runs of polyspike and slow wave discharges lasting between 1 and 7 seconds. Davidson et al. (1981) note that the effects of discharges can at times be fairly subtle.

Stores and Lwin (1981) also studied patients at home, in school or in hospital. In 21 cases they found that seizure activity predominated in waking, in 2 it predominated in sleep and in 5 it was equally distributed. In 5 children, seizure activity was clearly related to certain psychological or physiological factors. In individual patients these included; worry, boredom, drowsiness and physical activity. In one patient there was marked EEG and clinical improvement after ingestion of food although blood glucose levels were normal throughout.

Sato, Penry and Dreifuss (1976) monitored 5 patients each

for 2 days in hospital and 2 days at home. In 3 patients there was no significant difference between the amount of abnormality occurring whilst at home or in hospital. In one patient there were more discharges whilst in hospital and one had more whilst at home. Sato et al. note that although the total number of discharges varied the mean duration tended to remain unaltered.

Woods, Ives and Gloor (1975) made a similar observation whilst evaluating the use of ethosuximide. They recorded 2 days on and off the drug in each patient and found great intra-individual variability in the number of discharges but not in the mean duration. These authors also note that such variations in the frequency of occurrence of discharges make a 30 minute basic EEG totally inadequate as a method of assessing the number of attacks.

When assessing the effect of the environment on discharges several problems emerge. These have been recounted by Stores (1982). Firstly, one has to rely on the diligence of the person keeping the patient's diary sheet to correctly log the patient's actions. Secondly, close observation of the patient can itself influence results. Thirdly, ideally, a method of monitoring such factors as stress and heightened emotions in the patient is necessary. He notes that the galvanic skin response could be used in adults but is too obstrusive in children. In the past, heart rate had also been used but was prone to too many different variables.

Circadian variations in spike and wave activity have

interested many authors and these are discussed to a greater extent in a later section, with particular reference to sodium valproate.

Burr and Stefan (1981) note that several forms of rhythmicity may exist in the occurrence of attacks, eg. morpheic, matutinal and catemenial. Smith (1981) in fact describes a patient whose attacks appeared to be closely related to the menses. Furthermore, on non-menstrual days her basic EEG showed only occasional spike discharges in the right posterior temporal region. During her menses however, spiking also appeared in the left temporal region.

Several authors, eg. Docherty (1981); Davidson et al. (1981) and Blomquist and Zetterlund (1985) report that observers frequently underestimate the number of absences which patients appear to be experiencing when the ambulatory EEG tape is reviewed. Declerck et al. (1982a) found that subclinical paroxysms were commonly those which were too brief (no details of exact duration are given), or those which had a frequency of less than 2.5 or greater than 3.5 c.p.s. Such factors make ambulatory monitoring an ideal method of assessing the effect of therapy.

One of the earliest experiments of this kind is related by Ives, Wilkins, Jones et al. (1976). These authors recorded for 27 days in 2 to 5 day periods in one patient. Their aim was firstly, to assess the use of frosted glasses on the patient's extremely frequent pattern sensitive spike and wave, and secondly, to assess

the effect of the drug Taurine. Whilst the Taurine had no effect, the frosted glasses made a considerable impression on the number of discharges although considerable natural day to day variations were observed.

Other non-drug studies have included the effect of chronic cerebellar stimulation in patients with severe epilepsy (Docherty 1981) and the effect of a ketogenic diet in patients with severe myoclonic seizures (Stores 1979). Unfortunately, few details of these two studies are available.

Many drug studies include the use of sodium valproate and these again are discussed in more detail in a later section. Sefan et al. (1984) for example, gave 18 previously untreated patients an evening monodose of sodium valproate and found that this was an adequate therapeutic schedule for most patients. He notes also that serial ambulatory recordings are an ideal way of minimising the drug dose for each individual patient.

Blomquist and Zetterlund (1985) carried out baseline recordings and a further recording 3 months after beginning treatment with ethosuximide in 11 children. All showed 3 to 4 c.p.s. spike and wave activity associated with absence seizures. Seven children had no recall of their attacks whereas 3 were aware of them. Prior to therapy, parents estimated the number of attacks to be between 10 and 15 a day. In most cases this was an underestimation. After treatment had commenced however, it is argued that

ambulatory monitoring was not superior to long term observation by relatives at establishing freedom from discharges. In 8 patients total control was achieved both according to the EEG and by observation. In 3 patients there was a reduction of between 49 and 85% in discharges, in 2 patients attacks were still noticed and in one they were not. To assume that such findings imply that parental observation is superior to the EEG however, is not necessarily appropriate. In the first instance, the sample size is bias towards patients who are controlled and in the second instance it is far easier not to notice attacks than to notice them. A very strictly controlled study using trained observers would be necessary to prove such a point.

Introduction

There appears to be some disagreement in the literature with respect to the classification of non-epileptic attacks. In their book "Pseudoseizures" for example, Riley and Roy separate the sections dealing with pseudoseizures from other attacks of a psychiatric nature. Jeavons (1985) however, classifies hysteria as a psychiatric attack together with; outbursts, abnormal behaviour, reaction to events and habit spasms. In this context breathholding attacks could possibly be classed as psychiatric because they may be an abnormal reaction to events which are frightening or frustrating. Pond (1982) however, classifies breathholding as a biochemical disorder. In some cases, attacks of a psychiatric nature are classed as those symptoms of a psychiatric disorder which may be mistaken for epilepsy, eg. visual hallucinations.

To avoid problems of classification, the following section deals largely with each type of attack in turn. Pseudo-seizures are dealt with in some detail because many patients were referred in the present study with this as a possible diagnosis. Strictly speaking the term pseudoseizure should refer to attacks fulfilling the criterion for hysteria, however, many other non-epileptic attacks such as anxiety and panic may show similar symptomatology.

The aim of this section and the previous two sections is to outline some of the possible factors which differentiate epileptic seizures from non-epileptic attacks. To this

end a table has been compiled at the end of section 2.5. (Table 2.4).

Pseudoseizures - ictal patterns

Liske and Forster (1964) introduced the term 'pseudoseizure' to replace 'hysterical' seizure because they felt that the word 'hysterical' had become too broadly used and no longer conveyed specific information. Roy (1982) points out that the alternative term 'psychogenic seizure' could cause confusion as it is sometimes applied to epileptic attacks precipitated by psychological factors. This author also suggests that 'psychogenic' may imply conscious intent when in fact the motivation behind attacks may be unconscious. Conversely, the other possible term 'simulated' epilepsy suggests that the patient is simply malingering. Pseudoseizure is perhaps therefore the most appropriate term as it encompasses both the hysterical and the malingering.

Liske and Forster (1964) describe a pseudoseizure as "a clinical event which superficially resembles an epileptic attack, but, under closer scrutiny, is found lacking in an essential epileptic component, such as concomitant electroencephalographic dysrhythmia, or possessing a feature not compatible with epilepsy". Unfortunately however, it is not always possible to capture an attack during the EEG and there is continuing debate about the clinical features which distinguish a non-genuine attack from a truly epileptic one.

Gulick, Spinks and King (1982) divide pseudoseizures into 4 categories. Firstly, those with generalised stiffening,

jerking, trembling or thrashing which mimic generalised tonic-clonic convulsions. These kind of pseudoseizures they suggest, are the most common and were found in 55% of their patients. Secondly, they noted attacks consisting of unilateral motor activity resembling partial seizures. Thirdly, they observed attacks with multiple, more complicated phenomena suggestive of the automatisms seen in partial seizures and finally they observed attacks consisting mainly of reduced responsiveness and therefore resembling both partial and absence seizures.

They suggest that pseudoseizures of the first category were the easiest to differentiate from epileptic attacks. They and other authors, for example, Scott (1982) note that jerking occurs randomly in various parts of the body, sometimes switching from one leg to the opposite arm and often changing rhythm. Bouts of activity may be interspersed with pauses. Desai, Porter and Penry (1982) describe one patient who paused to wipe her face and then continued jerking, a feature which might characterise a partial seizure but not a generalised convulsion. Luther, McNamara, Carwile et al. (1982) found that 20% of their patients exhibited rolling of the body from side to side, again an unlikely concomitant of a generalised seizure.

A tonic phase characterised by arching of the back ('arc en cœrcle') was commonly seen in pseudoseizures by Desai et al. (1982) and also by other authors, but is less frequently seen in genuine epileptic seizures. These

authors also note the prevalence of pelvic thrusting, which is said by Gardner and Goldberg (1982) to have sexual implications, but they also point out that pelvic thrusting had been observed during one genuine partial seizure.

The onset of pseudoseizures is said to be often gradual with prolonged, non-specific warnings such as funny feelings, dizziness and tingling sensations whereas in epileptic attacks the aura usually lasts only seconds (Desai et al. 1982). Headache had been reported by several authors (Goodyer 1985; Cohen and Suter 1982 and Gubermann 1982) but this was usually a warning rather than a post-ictal phenomena. Stomach pain or sensations, chest pain and nausea have also been described by the same authors but can of course be symptoms of partial seizures or attacks arising from cardiac irregularities (Fowler 1984).

Vocalisation may be a feature of both epileptic and pseudo-seizures. Gulick, Spinks and King (1982) and Gardner and Goldberg (1982) report cries and screams from patients which occurred during attacks rather than at the beginning, as is often heard at the onset of a tonic-clonic seizure when air is expelled from the lungs. Liske and Forster (1964) report that some patients remained responsive to questions throughout attacks despite the appearance of generalised motor phenomena and Gulick et al. (1982) note that some patients produced slowed speech or delayed responses. Repetition of certain words and phrases has

been reported in both genuine and pseudo-epileptic attacks (eg. King and Ajmone Marsan 1977). At least two authors however, (Gulick et al. 1982 and Dreifuss, Holmes and Sackellares 1981) report obscene utterings during attacks which they suggest is a phenomena rarely heard during epileptic seizures.

Liske and Forster (1964) describe directed violence in one pseudoseizure and Dreifuss et al. (1981) observed frequent 'combative' behaviour in a group of 17 patients with pseudoseizures. Luther et al. (1982) recorded 5 attacks in which the patient struck out at objects or persons. Rodin (1982) however, points out that aggression during epileptic attacks or even during post-ictal confusional states is rarely seen. In an examination of 33 video recordings of seizures which were regarded as showing aggressive behaviour, a special committee of international investigators noted mainly 'non-directed motor activity' such as kicking or punching into the air. Only in one case was behaviour using 'physical force towards another person and yet not amounting to physical harm' noted. When violent behaviour does occur in genuine seizures, it may be the result of attempts to restrain patients (Scott 1982).

Self injury during pseudoseizures has been reported by many authors (Liske and Forster 1964; Guberman 1982; Cohen and Suter 1982) and should not be regarded as diagnostic of epilepsy. Cohen and Suter note that 12 of 51 patients

reported that they had bitten their tongues during attacks in the past and one patient sustained tongue lacerations from an attack recorded in the clinic which was induced by suggestion (most patients who reported tongue lacerations had had tongue blades inserted). Parsonage (1973) argues however, that teeth indentation marks are seen characteristically down one side of the tongue if sustained during an epileptic convulsion and Jeavons (1983) points out that the tongue may be bitten at the tip during a fall.

Gardner and Goldberg (1982) suggest that incontinence only occurs in epileptic seizures, a view not held by many authors including Desai et al. (1982) who noted urinary incontinence in two patients during observed pseudoseizures. Thirteen of Cohen and Suter's 51 patients reported incontinence in the past, and 2 were incontinent during induced attacks even though all patients were allowed to empty their bladder before the induction procedure. It should also be remembered that incontinence is quite common in syncopal attacks (Jeavons 1986, personal communication).

Changes in respiration may accompany pseudoseizures. Liske and Forster (1964) report breathholding in an adult until cyanosis was caused. Hyperventilation was a feature in 6 of 27 patients' attacks recorded by Gulick et al. (1982) whereas Desai et al. (1982) suggest that this is extremely uncommon in any genuine seizure type. Choking,

retching and grunting was a feature of attacks in 11 of Gulick et al's. patients. It is surprising, since this often tends to be the 'laymans' view of a convulsion, that salivation was only observed in one of their patients.

Several authors have studied the behaviour of the eyes during pseudoseizures. Rosenberg (1982) notes downward deviation of the eyes in patients feigning unconsciousness. When the eyes were held open and the head turned, the eyes made saccadic movements to the side facing the floor or alternatively they darted from side to side. In a truly comatose patient, Rosenberg states that there would be no movement of the eyes or smooth movement opposite to the direction of the head turn. He does concede that some partial seizures could cause deviation of the eyes to one side but suggests that this deviation would not always change when the head was turned. Gulick et al. (1982) also studied the eyes in their 27 patients and found; the eyes were closed in 14, open in 10 and open and closed in 3. Those with their eyes open showed a fixed position in 7 and normal movements in 6 even when there was tonic posturing. Three patients exhibited rapid blinking. Liske and Forster (1964) note that patients often avoid eye contact with observers of attacks and Luther et al. (1982) state that patients sometimes resisted efforts to lift the eye lids. Although this can also be found in true post-ictal confusional states (Scott 1982).

Automatisms resembling those seen in complex partial seizures were present in 29 episodes in 14 patients studied

by Gulick et al. (1982). Six patients looked about as if searching for something, 5 touched their heads as if in pain or confused, others walked around or moved objects, one cried, one made an obscene gesture and in 19 episodes there was swallowing, chewing or licking of the lips. These authors note that all automatisms occurred at the onset of the attack and were not inappropriate continuations of activities already initiated, as seen in some absence seizures (Penry, Porter and Dreifus 1975).

Conversely, Luther et al. (1982) observed automatisms in only 1 of 30 patients and this consisted of clawing of the left side of the face and clothing.

Eleven percent of patients studied by Gulick et al. (1982) showed unresponsiveness only, they state therefore that, on the basis of observation alone, these were indistinguishable from absences or complex partial seizures.

It has been suggested that a lack of post-ictal confusion may distinguish some genuine attacks from pseudoseizures (Mostofsky and Williams 1982).

However, Cohen and Suter (1982) reported post-ictal confusion in 38 of 51 patients and Desai et al. (1982) observed post-ictal confusion in 2 of 6 patients. Liske and Forster (1964) found headache or drowsiness in 3 of 9 patients. When there is no post-ictal state it should also be remembered that some brief partial seizures and

also absence seizures may be characterised by a rapid recovery (Goldensohn 1983).

One final phenomena observed by some authors is apparent "pseudoepileptic status". Guberman (1982) describes one patient whose status was resistant to intravenous phenytoin, diazepam or phenobarbital and was curarized and given assisted ventilation. This phenomena may therefore lead to potentially hazardous means when not recognised. Scott (1982) also describes a patient with a "large calcified hematoma on the forehead as a result of falls" who had previously been diagnosed as having status epilepticus. After prolonged hospital admission and the use of placebo it was found that all attacks were pseudoseizures.

Diagnosis of pseudoseizures

A family history of epilepsy may be a 'red-herring' leading to a mistaken diagnosis of epilepsy (Jeavons 1983; Guberman 1982). Desai et al. (1982) found that when questioned some patients had friends with epilepsy or had witnessed attacks in other people. It has also been noted that pseudoseizures may occur in members of paramedical professions. Liske and Forster (1964) found this in 2 patients and Gardner and Goldberg (1982) found this in one.

Mostofsky and Williams (1982) note that pseudoseizures

may develop in children and adolescents with various forms of organic brain dysfunction who are aware of the special attention gained from a seizure. This may partly account for the possible higher incidence of neurological problems in patients with pseudoseizures. Many patients therefore seem to have a template on which to mould their attacks. Liske and Forster (1964) also note that in some patients, pseudoseizures may evolve over a long period of time with a tendency to "accumulate the spectacular and to discard the prosaic or those features which were of low value in getting attention".

Associated neurological problems may also lead to a mistaken diagnosis of epilepsy. Cohen and Suter (1982) found evidence for neurological disease in 12 of their 51 patients without any particular disease being prevalent. Roy (1982) notes that between 40 and 64% of patients with hysteria have some organic brain dysfunction.

A history of febrile convulsions may also be a 'red-herring' (Jeavons 1983). Ross and Peckham (1983) found that approximately 2.4% of the population as a whole, suffer convulsions associated with fever in childhood and 94% of children never experience another afebrile seizure. This should not therefore be taken as an indication that later seizures are genuine.

Several authors have found an underlying psychiatric disorder in patients with pseudoseizures. Roy (1979) examined

22 patients and gave a clinical diagnosis of a current affective syndrome to 86% compared to 27% of a control group of patients with epilepsy. Sixty-four percent of the pseudoseizure group had attempted suicide in the past compared to 18% of the control group.

Krumholtz (1983) found the most frequent psychiatric diagnosis to be an acute conversion reaction with 44% of patients being depressed, 34% having hysterical personalities and 6% with 'schizoid' traits.

Six of 12 patients examined by Guberman (1982) had a past history of psychiatric disorders (mainly depression including attempted suicide) and in 6 the onset of attacks followed an "emotionally traumatic event". The importance of adverse life events has also been stressed by Gardner and Goldberg (1982) who found loss and separation to be a predisposing factor in 2 patients.

The diagnosis of acute conversion reaction suggested by many authors is best outlined by Roy (1982) who summarises the criteria given for this in the 'Diagnostic and statistical Manual of Mental Disorders' (1980). Firstly there should be some alteration in physical functioning which suggests a physical illness, but without a physical cause. This alteration should not be manifest as simply pain or a disturbance of sexual functioning and the patient should have no conscious control over it. Secondly, there should be one or more of the following

psychological factors associated with attacks; a precipitating personal trauma, the symptom should provide the patient with a means of avoiding something which he finds unpleasant and/or a means of gaining attention where ordinarily he would not. Finally, the symptom should not be part of a schizophrenic disorder.

As Desai et al. (1982) points out, it is often difficult to tell whether patients are malingering and have conscious control over attacks or whether they do satisfy the criteria for a conversion reaction and motivation is unconscious. Generally, when seizures are consciously and voluntarily feigned an easily recognisable goal is evident such as avoidance of military service (Mostofsky and Williams 1982).

The idea that pseudoseizures are rare in non-epileptic patients (Liske and Forster 1964) is no longer accepted. Table 2.3 shows that in adults, between 12 and 37% have an underlying seizure disorder although in children and adolescents this number may be higher. Dreifuss et al. (1981) and Roy (1982) note that in patients with epilepsy the pseudoseizures mimicked the genuine attacks.

Apart from King (1982) who gives no explanation for his findings, most authors have found an undoubted predisposition to pseudoseizures in females (Table 2.3), although in children the sexes may be more evenly matched.

Authors	Percentage with epilepsy	Percentage Females	Age (years)
Roy (1979)	36	95.5	mean 32
Dreifuss et al. (1981)	65	66	children
Cohen and Suter (1982)	12	78	67% 20-35
King et al. (1982)	25	44	mean 29
Guberman (1982)	looked at non-epileptics only	83	18-44
Krumholtz (1983)	37	71	most 15-35
Moffett and Scott (1983)	looked at patients with epilepsy only	94	mean 35
Goodyer (1985)	60	60	adolescents

TABLE 2.3 DETAILS OF PATIENTS WITH PSEUDOSEIZURES STUDIED BY OTHER AUTHORS

Pseudoseizures appear to be less common in children, although Finlayson and Lucas (1979) (cited in Cohen and Suter 1982) note pseudoseizures in one 4 year old. Goodyer (1985) suggests that in children there is more likely to be "diffuse anxiety states or disturbed behaviour" as opposed to depression which is often seen in adults. Table 2.3 in fact shows that the most common ages are the second and third decade of life.

Sexual maladjustment has also been suggested as being common in patients with pseudoseizures. Roy (1979) found this in 41% of patients and Guberman (1982) in 8%. Gardner and Goldberg (1982) citing Goodwin, Simms and Bergman (1979) suggest the possibility of incestuous experiences being a predisposing factor.

The inter-ictal EEG may lead to a false diagnosis of epilepsy in patients with pseudoseizures, particularly in those with a genuine seizure disorder and those with other neurological abnormalities. Roy (1982) advocates therefore, that non-specific minor abnormalities in the EEG should be reported with care. As Niedermeyer, Blumer, Holscher and Walker (1970) point out, patients whose attacks do not respond to normal levels of medication may be suffering from the toxic affects of anticonvulsants which may render the EEG abnormal. Overdosing with anticonvulsants may also disinhibit patients and therefore facilitate the occurrence of more pseudoseizures.

Niedermeyer et al. further state "control mechanisms fail and atavistic impulses bring forth the motor sequences of the hysterical seizure".

Scott (1982) suggests that the degree of inter-ictal EEG abnormality should be considered in light of the reported seizure frequency. With frequent genuine seizures the alpha frequency is low, it is disorganised and there is much slow activity. In patients who have frequent pseudoseizures and have had occasional partial seizures the alpha is well organised and there are small amounts of slow activity usually in temporal regions. Sonnen (1982) (citing Tsuboi 1981) further illustrates epileptiform EEG abnormalities such as spike and wave exist "approximately five times more frequent than clinical epilepsy".

It has been suggested that certain strategies which would not ordinarily evoke a genuine seizure can be used to evoke pseudoseizures. Cohen and Suter (1982) used an intravenous infusion of saline which they said was "medicine which would bring on a spell" and recorded the EEG during attacks in 48 of 57 patients. A further 3 patients had spontaneous attacks during the recording. A control group of 15 patients with genuine seizures was also studied, and none had attacks during this procedure.

Guberman (1982) told patients that attacks would be provoked by placing a tuning fork on the forehead and

sending "electric vibrations" through the brain. Using this method pseudoseizures were provoked in all 12 patients studied. Unusual precipitants of attacks have also been suggested as a sign that attacks are not epileptic. For example, Liske and Forster (1964) describe attacks brought on in one patient by eating a piece of cheese. It should be considered however, that some patients with reflex epilepsy can bring on or abort attacks by, for example, thinking of a particular idea (Scott 1982).

Similarly, measures which are unlikely to end genuine attacks such as hypnotic suggestion and saline infusion with suggestion (Cohen and Suter 1982) can end attacks. These authors also found that if they obstructed a patient's airway, attacks would be aborted. Several authors, eg. Liske and Forster (1964) noted extinction of attacks when observers left the room. Scott (1982) notes that a slap on the face, a loud noise or a dousing with water may end attacks although as he points out, such measures may be used to interrupt some absence seizures.

When attacks occur can often give some insight into their nature. Guberman (1982) notes that in only 'a few instances' did attacks occur in his 12 patients when they were alone or unobserved. Several occurred in the presence of family members, often with a group of people present and in emotionally stressful circumstances. Although as Scott (1982) points out, an elightened patient may be aware of the fact that the constant presence of an audience

may be diagnostic of pseudoseizures and simply lie about the circumstances of his attacks,

It has been suggested by Guberman (1982); Moffat (1983) and Roy (1982) that the features of pseudoseizures are variable whereas genuine seizures are stereotyped. Gulick et al. (1982) however, found "individual phenomena were almost identical in repeated episodes" even though the duration and sequence of events varied. Cohen and Suter (1982) also found that both the ictal and post-ictal patterns were stereotyped in their patients.

During attacks, several measures have been suggested which can aid diagnosis. Luther et al. (1982) demonstrated avoidance of painful stimuli such as the dropping of the patients own hand onto his face (particularly with implanted sphenoidal electrodes), or the dropping of the heel onto the shin. Desai et al. (1982) describe a patient who cried out when pinched although they also note that automatisms in response to external stimuli can occur in genuine seizures.

Normal pupillary responses were elicited in the patients examined by Guberman (1982), but Desai et al. (1982) point out that dilated pupils may not be an indication that attacks are genuine as this can also accompany strong sympathetic arousals. The movement of the eyes has already been discussed.

Eliciting the plantar responses has also been used as a diagnostic test, eg. Liske and Forster (1964). However, Scott (1982) (citing Hammond 1948), notes that an extensor plantar response was seen in one patient who was almost certainly having a pseudoseizure. This can occur also with various other neurological abnormalities.

It has been suggested that when abnormal discharges spread to areas of the brain such as the hypothalamus and the amygdala which mediate hormone release there will be concomitant changes in plasma hormone levels. Dana-Haeri, Trimble and Oxley (1983) showed that in patients with generalised seizures, prolactin levels were raised immediately and 20 minutes after the seizure. Fifty-nine percent of patients showed levels above 1,000uM/litre and 96% above 500uM/litre. Baseline levels returned within 60 minutes. Twenty minutes after complex partial seizures, elevated levels above 500uM/litre were observed in 78% of patients, but after simple partial seizures only one of 8 patients showed such a rise. These authors therefore advocate that partial seizures associated with loss of consciousness involve discharges in the hypothalamus and therefore are theoretically generalised and not partial. When attacks resembling complex partial seizures occur therefore, prolactin levels may be a useful diagnostic test as well as after more obviously generalised convulsions.

Hoppener, Rentmeester, Arnoldussen, Hulsman and Meijers (1982) found no difference in the increase in prolactin levels after generalised and complex partial seizures. They suggest that the ratio of the rise to the baseline value may be a more accurate indicator, particularly in patients with low baseline values. They found no significant increase in prolactin levels following absences, brief complex partial seizures (they do not give details of duration), pseudoseizures, or 20 minutes of heavy physical exercise (except in one of 4 patients with a value of 511uM/litre).

Conversely, Collins, Lanigan and Callaghan (1982) found elevated prolactin levels in patients who experienced generalised convulsions but no significant difference between patients who experienced partial seizures and patients with pseudoseizures. Unfortunately, this study did not include baseline data.

Recent work by Van Emde Boas and Endert (1985) has shown considerable spontaneous fluctuations in circadian profiles of prolactin levels and they point out that unless normal circadian values were known for particular patients, then post-ictal values would be of little validity.

Finally, probably the most useful indicator that attacks are not epileptic is the ictal EEG. Unfortunately however, even this has its shortcomings. Generally, during a

pseudoseizure the alpha rhythm blocks but within an instant of the end of the attack a well organised alpha reappears. Muscle potentials are often seen in bursts and do not resemble the spread of discharges seen in genuine seizures (Scott 1982). It is accepted however, that after partial seizures (particularly simple partial seizures), there may be a rapid return of normal rhythms (Klass 1975). Furthermore, Liske and Forster (1964) describe one case in which a burst of artefact during one recorded pseudoseizure was mistakenly diagnosed as epileptiform and led to a diagnosis of epilepsy until further ictal records were obtained. This had led most authors to diagnose pseudoseizures only on the basis of sections of EEG which were not obscured by artefact (eg. Gulick et al. 1982; Guberman 1982).

Most authors concede that in some partial seizures there may be no change in the scalp EEG. This assumption is often based on the work of Klass (1975). Ictal manifestations of partial seizures have been discussed at length in the appropriate section. It is assumed that seizures which involve loss of consciousness are usually associated with surface EEG changes, eg. King et al. (1982). Cohen and Suter (1982) however, warn against the misinterpretation of post-ictal EEG attenuation in pseudoseizures when the EEG gains have been reduced during attacks.

Desai et al. (1982) (citing Klass 1975) note that immediately after generalised tonic-clonic attacks the EEG

is almost always abnormal and is abnormal in half the cases of partial seizures.

Ambulatory monitoring in the diagnosis of pseudoseizures

Table 2.1 showed the results of various ambulatory EEG studies. Unfortunately, it is often stated that no EEG changes occurred during attacks but little information is given about possible alternative diagnoses.

Smith (1981) notes that the patient with pseudoseizures is "usually committed, with varying degrees of awareness, to resisting attempts to establish the psychogenic nature of such attacks, and is reluctant to engage in the frequently disturbing task of exploring feelings and problems. At this stage, ambulatory EEG monitoring can be of tactical value to the psycho-therapist".

One of the first documented cases of the use of 4 channel ambulatory EEG recording in a patient with possible pseudoseizures is given by Ives (1976). In this case the "hysterical" attack was found to be epileptic. Ives notes that "if no epileptogenic activity is seen, seizures cannot be ruled out because of lack of coverage and because some seizures can occur that are not reflected in the EEG recorded from the scalp". The first part of this statement was later to be questioned by Ebersole and Leroy (1983) who found that all 8 seizures, both generalised and partial, that were simultaneously recorded using 8 channel telemetry, were also recorded on a 3 or 4 channel

ambulatory EEG. Furthermore, these authors showed that inter-ictal EEG abnormalities were correctly lateralised and their anterior/posterior location was correctly diagnosed in 75% of cases. In order to achieve this they advocate careful montage design which has been discussed earlier.

Stores (1980) recorded attacks in 9 out of 37 patients. No EEG change was found in 3 patients and this was taken as a probable indication that attacks were not epileptic but due to other causes such as panic.

As well as looking at the ambulatory EEG, Ramsay (1981) looked at the value of the basic EEG. One hundred and thirty nine patients showed slowing of the basic EEG, some with lateralising features but 10 of these patients experienced attacks showing no EEG change. A further 6 patients who had normal basic EEGs also showed no EEG change during attacks. Ramsay concludes that the significance of negative findings in patients with an abnormal basic EEG is difficult to assess. He appears to conclude however, that all 16 patients were probably experiencing pseudo-seizures.

Docherty (1981) recorded attacks in 48 patients and found no obvious EEG change in 14 cases. It is noted that when artifacts due to movement obscured the EEG trace it was not possible to make a sound conclusion about the type of attack. It appears from his data however, that

although 6 attacks were obscured by muscle artefact, it was possible to decide upon the nature of the attack. Docherty further states that although lack of scalp representation of the EEG is a problem, it is unlikely that abnormality has been missed in the event of a "monotonously regular alpha rhythm at the time of the attack".

One of the few reported cases of both epileptic and pseudoseizures being recorded on the ambulatory EEG in the same patient is given by Davidson, Fleming and Kettles (1981). The pseudoseizure consisted of wild flailing of the limbs whereas the genuine seizure consisted of loss of posture and loss of consciousness. It is interesting that in this case the pseudoseizure did not appear to mimic the epileptic attack. Ten of Davidson et al's. patients were diagnosed as having possible pseudoseizures, 4 patients experienced attacks which showed no abnormality in the ambulatory EEG and were diagnosed as hysterical. Of the remaining attacks which showed no EEG or ECG abnormality no possible aetiology is given.

Ives, Hausser, Woods and Anderman (1981) also studied patients in whom attacks were thought to be hysterical or of psychological origin.

Twenty seven had normal or non-specifically abnormal basic EEGs and 13 had EEGs showing inter-ictal epileptic

activity but had bizarre attacks of uncertain aetiology. Of the first group, 16 experienced attacks and 14 showed no abnormality. In the second group six experienced attacks and 3 showed no abnormality, thus providing further evidence that epileptogenic abnormalities can be found in the basic EEG of patients with pseudoseizures, (there is no indication that these patients also had genuine seizures).

In the same series of patients who showed no EEG change, the descriptions of attacks included "small absence-like attacks, dizzy spells, shaking, loss of consciousness only, and loss of consciousness with jerking, although not all of these attacks could be labelled as pseudoseizures.

Bekovic, Bladin, Conneely, Gossat, Symington and Vajda (1984) studied a total of 87 patients and recorded 40 patients' attacks. Twelve patients were found to have pseudoseizures and 50% of these had genuine seizures also. Two patients strongly suspected of having pseudoseizures, showed focal EEG abnormalities during attacks.

Oxley, Roberts, Dana-Haeri and Trimble (1981) carried out ambulatory monitoring in 2 patients with mixed attacks (both epileptic and pseudoseizures) and also in 7 patients with pseudoseizures only. Diagnosis was made on the basis of "any history of psychiatric symptoms and evidence of past conversion hysteria or personality disorder". When attacks were actually recorded none of the patients with

pseudoseizures showed epileptic activity and in the patients with mixed attacks two exhibited both kinds.

Oxley et al. measured prolactin levels at 5, 20 and 80 minutes after each attack. None of the patients with pseudoseizures only, showed elevated levels. One patient with mixed attacks showed an elevated serum level after a non-epileptic attack. This subject showed continuous epileptic activity in the background record and it was later found that he had elevated prolactin levels which did not conform to a normal decay time.

A control group of 9 patients with epilepsy showed significant rises in prolactin after tonic-clonic seizures but not after attacks which were described as, "tonic and semipurposful, vacant - semipurposful (2 patients), tonic-atonic (2 patients), wild movements with incontinence and cry with semipurposful movements".

Oxley et al. conclude that prolactin levels were of a lesser value in the diagnosis of non-epileptic attacks. The concordance between the psychiatric opinion and the absence of changes in the EEG would, they say, not only exclude epilepsy but suggest a diagnosis of pseudoseizures.

Syncope

Noble (1981) describes syncope as "a transient loss of consciousness of abrupt onset, resulting from an impairment

in cerebral metabolism. Such an impairment results from a brief interruption of the cerebral circulation or from the shortage of required energy substrates, ie. glucose and oxygen, which are constituents of the blood delivered to the brain".

Reduced blood flow to the brain may be the result of several different factors. These are well reviewed by Riley (1982). He describes reflex syncope and syncope due to cardiac causes.

Reflex syncope can be brought about by pressure on the carotid sinus, this stimulates the vagal nerve which slows the pulse and reduces cardiac output. In predisposed subjects attacks can arise from a sudden neck turn, shaving and tight collars. Jeavons (1975) describes syncope in a child whilst having her hair brushed and holding her head back.

Ocular compression will also stimulate vagal receptors and cause syncope. Gastaut and Fischer-Williams (1957) used this test to provoke syncopal episodes in 71 patients. They state that patients prone to syncope have an unstable autonomic nervous system with excessive parasympathetic reactions. Amongst the causes of syncope in their patients were, emotion, pain, standing for long periods and fasting although the latter was probably due to a low blood sugar level. They also describe micturition syncope which commonly occurs in some males after arising quickly in the night when the blood pressure is at its lowest.

The parasympathetic activity of passing urine adds to the other factors and causes syncope.

The valsalvar manoeuvre (forced expiration against a closed glottis) will cause an increase in intrathoracic pressure and a subsequent reduction in cardiac output (Lai and Ziegler 1983). Gastaut, Broughton and Germano de Leo (1982) report compulsive self-induced syncope using the valsalvar manoeuvre in 3 mentally retarded children. One child had previously been diagnosed as having absence seizures, one as having unilateral clonic seizures and one as having myoclonic seizures.

Cardiac causes of syncope can arise from Stokes Adams attacks or complete heart block. Alternatively, if the heart is unable to compensate for vasodilation caused by exercise or a sudden change in posture there may be a sudden drop in blood pressure resulting in syncope. Finally, an obstruction of outflow from the heart or into the brain such as a thrombus may cause syncope, possibly only when certain postures are assumed (Riley 1982).

The differential diagnosis of epilepsy and syncope may be complicated by several factors. Firstly, the initial phase of the attack prior to loss of consciousness may consist of blurred vision, vertigo, tinnitus or echoing noises. If this onset is particularly prolonged the subject may feel 'dreamy', experience a feeling of derealisation or even hallucinate. Such symptoms are particularly likely to be confused with simple partial

seizures (Riley 1982). Fowler (1984) describes a case in which a 74 year old patient experienced a weak feeling in the chest and neck followed by loss of consciousness and sometimes clonic hand movements. He was treated for 3 years with AEDs. Finally, ambulatory ECG revealed a third degree heart block during an attack. In another patient a similar episode was preceded by a hot flushed facial aura.

Secondly, if this initial phase of the attack is followed by loss of consciousness with cardiac arrest (some attacks may arise from a drop in blood pressure without cardiac arrest), lasting for longer than 13 seconds then other symptoms which may be confused with tonic-clonic seizures are seen. These are isolated generalised myoclonic jerks and tonic extension which may be more marked on one side of the body than the other and result in head deviation (Gastaut and Fischer Williams 1957).

Thirdly, as the patient comes around, very occasionally but particularly after prolonged attacks, he may be confused, sleepy and experience weakness, similar to a post-ictal state (Riley 1982).

Certain features however, may aid the diagnosis. Firstly, patients are rarely propelled to the floor as in a convulsion, but sink down slowly and they also become pale and perspire. Secondly, there is no typical tonic-clonic phase to the attack (Riley 1982). Finally, the EEG during

attacks can also be diagnostic.

Gastaut and Fischer Williams (1957) showed that if there was cardiac arrest lasting for longer than 7 seconds bilateral slow waves appeared (never accompanied by spiking) predominantly in frontal regions. There was never any EEG change associated with the myoclonic jerks and when the tonic spasms occurred, usually after about 14 seconds, the EEG was flat. As the heart restarted more slow activity began to appear and at times predominated over a disorganised alpha rhythm for several minutes after the attack had ceased. *more recent work has been carried out by Stephenson.*

Confusion has arisen in the past in that the myoclonic jerks have led to the term 'anoxic seizure'. Gastaut and Fischer Williams argue against such a term due to the lack of EEG seizure activity during attacks.

It has however, been reported, that repeated self-induced syncope can cause damage to sensitive areas of the brain such as the hippocampus and give rise to an epileptic focus (Lai and Ziegler 1983).

Rutter and Southall (1985) note that there may be a familial predisposition to syncope as well as epilepsy. They describe a mother and 3 children with "disordered sympathetic innervation of the heart" causing ventricular arrhythmias. All four were treated unsuccessfully with anticonvulsants. Three children died before the correct

diagnosis was made, the mother died a year later. Three remaining children were found to have similar arrhythmias and treated successfully.

Ambulatory monitoring in the diagnosis of syncope and cardiac irregularities

Ives (1976) was one of the first authors to advocate combined EEG/ECG ambulatory monitoring in patients with attacks of possible cardiac origin. He gives an account of a 45 year old man with "fainting spells" which were shown to be associated with rhythmic slow activity in the EEG but no ECG change.

A patient who experienced a feeling of faintness followed by loss of consciousness and slight twitching of the limbs is described by Docherty (1981). At the time of the attack the EEG was obscured by muscle and movement artefact but the ECG showed a 40 second episode of asystole. Combined EEG and ECG was recorded in 16 patients but only this one showed an ECG abnormality during an attack, it is not clear whether other attacks were recorded in these patients.

Callaghan and McCarthy (1981) made a provisional diagnosis of syncope in 18 patients and cardiac problems in 3. Forty six patients were studied in all. During ambulatory monitoring, 6 of the 18 were found to have epilepsy and in the other 3 the diagnosis was confirmed.

It is suggested that errors in diagnosis may have arisen due to the unreliability of eye witness accounts of attacks. A cardiac basis was therefore found to account for attacks in 20% of patients in whom this was suspected.

A detailed account of the EEG during syncopal attacks is given by Lai and Ziegler (1981). The clinical description of the attack was, "found unresponsive, slumped in his bed with twitching of facial muscles". The EEG prior to a 5.5 second period of asystole was normal. During the asystole slow waves at 1.5-3cps of varying amplitude appeared in the EEG. After approximately 25 seconds the EEG returned to the baseline level.

Blumhardt and Oozeer (1981) describe 2 patients in whom the background history and the EEG may have led to a misdiagnosis. Eleven of the 68 patients experienced typical attacks but only 2 showed positive diagnostic abnormalities. One patient experienced attacks consisting of "nausea and weak and clammy hands". She would then slump, gripping onto observers but remain "limp with eyes closed, rapid respiration, trembling and pallor". The diagnosis was further confused by a twin sister who had experienced similar dizzy spells and had been treated successfully with a demand pacemaker. Ambulatory EEG recording revealed a right sided focal seizure.

The second patient had previously been diagnosed as having complex partial seizures. Symptoms consisted of "fear,

sweating, blurred vision, bursting and thumping sensations in the chest, a reluctance to talk and a sensation of falling lasting up to 2 hours". The diagnosis may have been further confused by the presence of asymptomatic right sided theta activity in the basic EEG. Combined ambulatory EEG and ECG recording revealed long bursts of "ventricular, bigeminal rhythm and no EEG change".

The work of Green, Scales, Nealis and King (1984) suggests that ECG recording may be more valuable in adults rather than children. They examined background EEG and ECG abnormalities in 100 patients. They divided patients into 3 groups - 0-40 years, 40-60 years and 60 years and over. In the first group, 17% of patients showed abnormal ECG activity whereas this rose to 38% in the last group. Although they do not give specific details of children and adolescents they note that "0-20 years, seizure most suspect and 60 and above ECG abnormality most suspect".

Blumhardt (1985) strongly advocates that ECG recording should be used routinely in patients referred for ambulatory EEG investigations. His data however, suggests that in a totally unselected group of patients with episodes of disturbed consciousness the yield from ECG recording may be much lower than that of the EEG.

In a group of 145 patients, 30 typical attacks were recorded in 29 patients. In 4 patients seizure activity

was observed, in 14 there was no EEG or ECG change, in 11 the EEG was equivocal but the ECG showed no change and in only one was there a cardiac arrhythmia. Thus, in this group of patients, unselected on the basis of attack frequency and unselected on the basis of whether the history was suggestive of cardiac problems or epilepsy, only 3% showed an ECG change during an attack.

It is interesting that the number of cases in which the EEG was equivocal was 27%. This was higher than any other author (see Table 2.1) and one must question whether this arose due to the use of only 2 EEG channels.

Blumhardt further illustrates that the presence of a known "neurological lesion" would increase the likelihood of recording an epileptic phenomena by fourfold. The presence of a known "cardiac lesion" however, increased the likelihood of recording a cardiac arrhythmia two-fold and in fact was equally as likely to produce an epileptic attack. Unfortunately however, these figures are based on very low patient numbers.

In a second group of 23 patients with probable epileptic attacks and other symptoms of unknown origin, only one patient exhibited a cardiac arrhythmia and this was associated with a "minor event unrelated to the original problem". In fact in 4 patients with a possible diagnosis of syncopal attacks or attacks of cardiac origin, one experienced a seizure and 3 showed no EEG or ECG change.

This work therefore reveals a surprisingly low level of cardiac problems in both unselected patients and patients thought to have possible syncope or cardiac irregularities. Callaghan and McCarthy also showed that even in patients thought likely to be suffering from syncope, 33% actually had epilepsy. Unfortunately, Callaghan and McCarthy do not give details of whether patients had previously undergone other ECG investigations and one must question whether such investigations would have answered the question equally effectively.

In conclusion, it would appear that in an unselected group of patients, ECG recording may provide little information and it may provide even less information in children. In patients in whom a cardiac origin is strongly suspected then there may be a need for an additional ECG channel but this may cause problems in the interpretation of the EEG when only 2 EEG channels are available. It may be advisable therefore, to dispense with the time/event channel instead and substitute this for ECG. All studies mentioned used a 4 channel recorder, using 8 channels, scalp representation should be less of a problem. The presence of cardiac irregularities during epileptic seizures (Blumhardt et al. 1986) requires careful consideration however, and this has been discussed in the section dealing with partial seizures.

Hyperventilation

Riley (1982) suggests that hyperventilation is seen most commonly in adolescents and young adults. Patients complain of an inability to breath deeply enough and the attack is often precipitated by emotional stress. During the attack, breathing appears to be at the usual rate but there is "heaving of the upper sternum and lack of lateral costal expansion" similar to when a person sighs. According to Riley, over-breathing can occur as a manifestation of some complex partial seizures, but in this case the breathing is more forced and is associated with movement of the abdominal muscles.

Hyperventilation can produce; tetany with spasms in the limbs, dizziness, a sense of unreality; blurred vision, tingling sensations and tachycardia. Six to 15% of patients actually lose consciousness. Particularly when consciousness is lost, these symptoms may be mistaken for auras (Riley 1982).

Joorabchi(1977) argues that hyperventilation may also be common in children. He studied 50 children, many of whom had been given a possible diagnosis of heart disease. All 50 patients experienced chest pain or discomfort. In 16, pain was worse in the legs, only five complained mainly of a breathing problem and others were referred due to fainting and palpitations.

Numbness, dizziness and pallor were frequently associated with attacks and 22% also lost consciousness.

The EEG recorded during attacks shows only high voltage diffuse slow waves without spiking (Riley 1982).

Associated findings in the children examined by Joorabchi were: frequent irritability, depression, anxiety and a high proportion of "growing pains", headaches and abdominal pain.

Breathholding attacks

Jeavons (1975) notes that breathholding attacks in children are precipitated by pain, injury, fright or frustration and such a precipitant can often be diagnostic. He notes that the basic EEG is usually normal but the child often resents the procedure and this may bring on an attack.

Bower (1981) describes two types of breathholding attacks in children. Firstly, cyanotic breathholding attacks brought on by a valsalvar manoeuvre. The child goes into a tonic posture, he is cyanosed, his eyes may roll upwards and he slumps apparently lifeless. Very occasionally there may be some clonic movements and incontinence. The attack lasts only seconds and the child does not produce post-ictal symptoms although he may be quiet afterwards.

Pallid breathholding attacks (or pallid syncope) usually occur after a frightening event such as an unexpected blow to the head or immunisation. There may be some asystole during attacks and they can last for several seconds. The child becomes limp, pale and unconscious as if dead. The EEG during attacks is similar to that described for syncope.

Bower (1981) also discusses apnoea limpness and pallor occurring in infants after a feed. He suggests that this may be brought on by aspiration of milk into the larynx causing vagal asystole.

Transient ischaemic attacks

Pond (1982) describes attacks which are due to cerebrovascular causes. If the basilar artery is occluded there may be transient disturbances of consciousness with paralysis and speech arrest, attacks can often last for hours rather than for the brief period of a seizure.

In old people such disturbances in blood supply may cause drop attacks or senile falls (Pond 1982). The patient suddenly finds his legs give way beneath him and this is followed by a very brief period of confusion or amnesia. These attacks commonly arise from a kinking in the vertebral artery when the patient reaches up to touch something.

Vertigo

A relatively rare phenomena is benign vertigo of childhood. The child experiences a feeling of rotation or falling (which is the best guide to diagnosis), he may reach for support or lie down but does not lose consciousness. There may also be nausea, sweating and nystagmus and the child appears drunk (Bower 1981). This author also states that attacks may begin after the first year and cease at school age, no medication is effective at controlling attacks.

In adult patients who suffer from Meniere's disease, sudden attacks of giddiness may be so severe as to cause loss of posture and may also be misdiagnosed as epileptic (Pond 1982).

Migraine

Attacks of migraine, caused by cerebro-vascular spasm may give rise to focal symptoms not unlike those of focal epileptic attacks (Pond 1982). Jeavons (1983) describes the case of a child in whom attacks consisted of "a left sided headache with hemianopia and tunnel vision and parasthesia in the left hand".

Other attacks in childhood

Night terrors may be confused with partial seizures

occurring during sleep, mainly because the child may take 15 to 20 minutes to recover (Bower 1981). If the EEG is recorded it can be seen that night terrors occur in non-REM sleep and there is no epileptic activity in the EEG.

Jeavons (1975) describes a case in which "daydreams" were mistakenly diagnosed as absence seizures. In this particular case the child frowned during attacks, a symptom which is said not to occur during absence seizures. In most cases, hyperventilation will bring on a true absence seizure and in 70% of patients the basic EEG is diagnostic (Bower 1981).

Bower (1981) also describes gratification phenomena in children of 2 to 3 years. The child assumes a certain posture, tenses various muscle groups and holds his breath. There may be a slight tremor and the child is "far off" but obviously not unconscious and the attack can be aborted by talking to, or touching the child.

Ambulatory monitoring in the diagnosis of non-epileptic attacks in children

Eyre and Crawford (1981) describe the use of ambulatory monitoring in neonates with neurological abnormalities who showed repeated episodes of abnormal behaviour.

They note that seizures in the neonate are often atypical including -"jerking of the eyes, tonic posturing of the limbs, sucking, apnoea and respiratory pattern abnormalities". They recorded attacks in 9 babies and found 3 showed no abnormality, 2 had seizures, 1 had EEG changes of the type associated with hypoxia and 1 showed inter-ictal abnormalities not associated with attacks. The use of ambulatory EEG and ECG is at present being assessed as a prognostic indicator in seriously ill neonates by Dr Eyre.

Attacks of disturbed behaviour were investigated in 76 children by Forrest and Crawford (1981). Eighteen children experienced attacks of episodic behaviour but no seizure activity was seen. The final diagnosis consisted of such problems as: imaginary companion, depersonalisation syndrome, habit spasm, anxiety state (5 children), emotional disorder, sleep disorder (3 children), stereotypies and simulated seizure (5 children). Simulated seizures and sleep disorders were only present in patients with a previous history of epilepsy.

Hall (1981) assessed the indications for ambulatory monitoring in paediatric practice. These included, frequent falls, poor school performance, possible paroxysmal tachycardia and sensori-neural deafness (with possible absences). He notes that ambulatory monitoring seemed to have an inhibiting effect on breathholding attacks.

It is notable that both Forrest and Crawford (1981) and Hall (1981) recommend the use of an ECG channel in children, but no cardiac irregularities are mentioned in either series.

Bachman (1984) also used ambulatory EEG and ECG monitoring to diagnose "spells" in 23 children without an additional history of epilepsy and 11 with an additional history of epilepsy. Attacks which proved to be epileptic consisted of:

jerking right side for hours
numb on right, back pain and altered speech
daytime and nocturnal enuresis
episodic dizziness
pain in legs, fall without loss of
consciousness

Attacks which did not show seizure activity were described as:

rolling stomach, holding breath and
pupils dilated
headache, abdominal pain and falling
jerking with a noise
staring spells
dizzy and blackout
unsteady, eye rolling, facial movements
jerking in sleep
stiff neck, hoarse and protrusion of tongue

numb and weak left side, and sweating
staring, grabs hand, does not talk, but
understands, gagging and rigid
jerking in sleep, encopresis

The variety of symptoms in these two groups illustrates the considerable difficulty in diagnosis. In 38% of children with an additional history of epilepsy the spell proved to be epileptic whereas only 18% of the remaining group proved to have seizures.

Again it is noted that one channel was used for ECG recording but none of the spells were accompanied by a cardiac arrhythmia.

Psychiatric symptoms

Some psychiatric symptoms such as the episodic mutism; immobility and outbursts of violence seen in catatonia may be sometimes mistaken for epilepsy (Pond 1982). However, epileptic attacks are usually brief whereas such psychiatric symptoms can last for hours or days. We have had patients referred to our clinic with compulsive behaviour, depersonalisation and visual or auditory hallucinations.

Jeavons (1983) notes also that episodic disturbances of behaviour in children such as aggression, can be mistaken for epilepsy but usually a precipitating factor can be found. Some habitual behaviours in children with behaviour

disturbances, for example, grimacing and giggling innapropriately have been a source of referral to our own department.

Jeavons (1983) also suggests that some normal physiological or psychological disturbances can sometimes appear similar to partial seizures, eg. palpitations, butterflies in the stomach, *déjà vu*, hypnagogic hallucinations and myoclonic jerks on falling asleep.

Under the list of psychiatric disturbances perhaps the acute anxiety attack should also be included. Such attacks may be accompanied by perspiring, palpitations, tremor and hyperventilation. Throughout the attack there is however, keen preservation of consciousness (Desai et al. 1982).

Jeavons (1985) discusses the differential diagnosis of psychiatric disorders and epilepsy in 56 children and 85 adults. In children "episodic outbursts" were the most common alternative diagnosis and in adulty anxiety attacks were more common. In an average of 8% of patients, attacks were regarded as a reaction to certain events, for example, those causing frustration.

Pseudoseizures were considered to be the alternative diagnosis in 4 and 5% of children and adults respectively.

Pond (1982) notes that withdrawal from alcohol can cause isolated seizures and often results in referral to

casualty departments. Barbiturate withdrawal can also have the same effect. Pond also notes that "drowsy, amnesic episodes, blackouts, inexplicable falls and apparently psychogenic fugue states" may also suggest some kind of drug abuse.

Goodyer (1985) isolated the abuse of solvents to be the cause of supposed pseudoseizures in one patient. A blood sample after one attack revealed D-toluene and the attack was therefore assigned to an hypotensive episode causing syncope after 'glue-sniffing'.

Fictitious epilepsy

Meadows (1984) describes 36 cases in which epileptic seizures had been invented by a patient's relative, that relative usually being the mother. Seizures often occurred at night, in those during which another observer was said to have been present, this was subsequently denied by that person. In 11 cases, seizures were actually caused by the mother by partial suffocation, pressure on the carotid sinus, or drug abuse.

Patients had often experienced extensive investigative procedures and had been treated unsuccessfully with numerous anticonvulsants. Several continued into adulthood believing themselves to have seizures and others developed various other false illnesses.

Meadow argues that fictitious epilepsy is not rare, mainly because epilepsy is easy to fabricate. Enlightened parents realise that there are no entirely diagnostically conclusive investigations and the physician often has to rely solely on the clinical history.

Ambulatory monitoring in the diagnosis of psychiatric symptoms

Stores (1979) describes a 30 year old female with 'episodic schizophrenic-like episodes' and also a history of secondary generalised tonic-clonic seizures. New symptoms appeared in this patient consisting of attacks of slumping and shaking of the head and limbs. At first these attacks were thought to be "attention seeking" but ambulatory EEG recording revealed spike and wave activity.

Smith (1981) notes that when new episodic symptoms appear in patients with a history of epilepsy they are often referred for psychiatric assessment in the belief that they are of a neurotic nature. He describes 2 cases. The first is a 24 year old nurse with a history of complex partial seizures since the age of 10 years. New symptoms consisted of brief episodes of anxiety, fear, unpleasant olfactory sensations and slight blurring of consciousness. The patient recognised the possible 'psychogenic' nature of attacks as she was also mildly depressed. Ambulatory EEG recording revealed a non-specific abnormality during

one of several attacks but the general impression was that attacks were not of epileptic origin. There was a subsequent reduction in the level of anxiety and also in the number of episodes, although she only became symptom free when medication was slightly adjusted.

The second case described by Smith is a 32 year old mentally handicapped man with "severe epilepsy and schizophreniform psychotic episodes". New symptoms consisted of staring, grunting and turning his head to the right. Ambulatory recording revealed spike and wave activity during these episodes.

Epileptic attacks not identified

Just as some episodic disturbances of behaviour may be mistakenly diagnosed as epilepsy, some epileptic attacks may not be recognised as such. Two of these are described by Bower (1981).

Infantile spasms or salaam spasms may give the impression that the child is attempting to sit up or doubling up with colic. In almost all patients the EEG shows epileptic features and in a large percentage there will be hypsarrhythmia.

Myoclonic atstatic epilepsy occurs in children over 2 years of age. The child appears to be flung suddenly forward or back or may collapse due to loss of muscle tone. There is little or no loss of consciousness and

the child immediately gets up. Again, in most cases the basic EEG is abnormal.

Davies (1982) describes epileptic seizures during sleep in 2 patients which had been misdiagnosed as behaviour problems. One child was inattentive at school, fell asleep in class, was irritable and often complained of headache on waking. The other child was difficult to arouse and when woken was prone to temper tantrums and destructive behaviour. In both cases the waking EEG was normal but the sleep EEG showed focal abnormalities.

Lesser et al. (1983) describe a case of a sensory seizure which could easily have been mistaken for a pseudoseizure. Attacks consisted of a "chill" affecting the left knee, shoulder, arm, hip, rectum and sometimes spreading to the right knee. There was no alteration in consciousness. Suggestion was used to induce an attack whilst the EEG was being recorded. The procedure was successful and an attack was recorded which showed "rhythmic left temporal theta activity". CT scan and biopsy revealed a left temporal glioblastoma.

Lesser et al. conclude that "bilateral symptoms with preserved consciousness do not exclude the possibility of an epileptic etiology". They further warn that suggestion should not be used to diagnose pseudoseizures without EEG monitoring.

In conclusion, Jeavons (1985) notes that although

ambulatory monitoring may help in the differentiation of non-epileptic attacks, the ultimate diagnosis depends on a "detailed history including an account from an observer".

Findings	Pseudoseizures	Other non-epileptic attacks	Partial seizures	Absence seizures	Primary generalized tonic-clonic
motor phenomena	stiffening, jerking, random, sporadic	syncope & stiffening } vaso vagal } clonic hyperventilation } stiffening } spasms } breath-holding } stiffening } clonic jerks } gratification } tense, } slight tremor } phenomena }	unilateral and spreading	eyelid flicker or twitching - increased tone - loss of tone -	set pattern and generalised
autonomic	?	benign } nausea } vertigo } pallor } syncope } sweating } breathholding } tremor } hyperventilation } acute anxiety } attacks }	common especially epigastric blushing, salivation, pilo-erection	pallor, flushing, perpiration, salivation	
Incontinence	common	syncope- quite common breathholding- occasionally	sometimes	rare	common
Vertiginous symptoms	?	benign vertigo syncope menieres hyperventilation	sometimes	-	-
psychic disturbances	prolonged	psychiatric illness	brief fear and deja-vu common	-	-
variability of symptoms	same phenomena vary in sequence	variable	sometimes	common combination of mild clonic and automatisms and loss of tone	set pattern
vocalisation	various, may be obscurities	?	repetitive coherent and incoherent, speech arrest	mumbling or humming	

TABLE 2.4 ICTAL PATTERNS OF EPILEPTIC AND NON-EPILEPTIC ATTACKS

Findings	Pseudoseizures	Other non-epileptic attacks	Partial seizures	Absence seizures	Primary generalized tonic-clonic
visual/auditory hallucinations and illusions	?	psychiatric illness, syncope	simple - in 16-18% complicated - rare	-	-
other sensory disturbances	prolonged	hyperventilation - tingling, numbness, migraine - paras-thesia, visual disturbances	common - numbness or tingling less common - olfactory or gustatory	-	-
change in respiration	?	acute panic attack - hyperventilation, breathholding, hyperventilation	rare in complex partial	brief interruption	may cease from tonic phase till end
headache	often as warning or during attack	migraine	?	-	post-ictal
automatisms	never perseverative	habit spasms	63% de novo reactive, perseverative.	de-novo, reactive, perseverative.	reactive in post-ictal phase
injury	commonly reported	faint-tongue bitten at tip during fall	?	?	common, tongue bitten down side
aggression	common	reactive outbursts	rare	-	only on recovery in response to restraint
warning	common, prolonged non-specific	syncope - blurred vision, vertigo, tinnitus, dreamy	In 40-50% and brief, 56% of patients more than one type	-	-
post-ictal state	33-75%	breathholding - quiet night terrors - 20 mins to recover	most complex partial unless very brief	-	retrograde amnesia, slow, confused, headache, sleep, limbs ache
eyes	downward deviation avoidance of eye contact, rapid blinking	breathholding-roll up benign vertigo-nystagmus	deviation	roll upwards	deviation
duration	varies	?	minutes	seconds	minutes

TABLE 2.4 (continued)

Findings	Pseudo-seizures	Other non-epileptic attacks	Partial seizure	Absence seizure	Primary generalised tonic-clonic
reaction to stimuli	avoidance of pain delayed or slowed answers	sometimes	only towards end, reactive automatisms	reactive automatisms, unresponsive can abort	-
precipitants	unusual types, stress, with audience	syncope — pain, emotion standing, micturition, valsalva anxiety — stress, breath — injury holding frustration	rare	? stress ? boredom 70% hyper-ventilation	flicker sleep
EEG during attack	normal/artefact	syncope, } slowing vaso vagal } flattening cardiac }	abnormal most complex partial, abnormal 10% simple partial	abnormal	abnormal
ECG during attack	tachycardia preceding symptoms	syncope, } asystole vaso vagal } cardiac } hyperventilation-tachycardia	tachycardia, then irregular	? tachycardia	tachycardia, then irregular

TABLE 2.4 (continued)

Before ambulatory monitoring could be shown to be useful in recording sleep in the home, the technique required validation. Wilkinson and Mullaney (1976) using normal volunteers compared recordings made on the cassette to those made by conventional means, recordings were made simultaneously. A good correlation was obtained between the two types of recording using visual scoring techniques.

It was also necessary to show that ambulatory recording had any real advantage over laboratory recording since if patients found it impossible to sleep wearing the apparatus, little clinical information would be gained. Compared to sleep in the laboratory, Korner, Ladurner, Flooh, Reinhart, Wolf and Lechner (1982) found that the ambulatory sleep record showed a higher amount of total sleep time and time in bed. Subjects also preferred it. Riley and Peterson (1983) found also, that compared to laboratory recording sleep onset and REM onset times were shorter, REM duration was longer and there were less awakenings during the night.

It would seem therefore that when required, ambulatory monitoring could be a useful substitute for laboratory sleep recording. The need for all night sleep recording may occur in patients with certain types of epilepsy whose attacks occur just before waking or even just

after waking. Furthermore, in some patients with normal normal waking EEGs, the sleep EEG may provide more useful information, often however, patients find it difficult to sleep in the laboratory.

Janz (1974) carried out an extensive review of the literature concerning the relationship between types of epilepsy and the sleep/wake cycle. Although his method of classification is sometimes difficult to relate to the 1981 classification of seizures, a general overview is presented below.

He divides seizures into 3 types. The first occur during waking only, especially just after waking in the morning. The second occur only during sleep especially just after going to sleep or just prior to waking. Finally, a third type occur randomly and are not contingent on the sleep/wake cycle.

Epilepsies with cortical seizures without secondarily generalised tonic-clonic attacks (said to include partial seizures with motor, adverse or sensory symptomatology) occur either randomly or mainly in sleep. Such attacks are rare just after waking. According to Janz only a very small percentage who have normal waking EEGs will show inter-ictal abnormality during sleep.

Partial seizures with psychic symptomatology are said to occur according to either of the 3 patterns. The percentage increase in abnormality observed during sleep

in patients whose waking EEGs are normal is said to vary from between 7% and 68% depending on the author and extent of waking investigations.

The distribution of tonic-clonic seizures appears to vary depending on the aetiology. Hereditary or idiopathic seizures are said to occur either during waking only, or sleep only but rarely randomly. Tonic-clonic seizures which are symptomatic occur either randomly or during sleep only. In patients with tonic-clonic seizures whose attacks only occur in sleep, the sleep EEG is said to show a considerable increase in abnormality. However, in patients who have tonic-clonic seizures in waking only, there is little increase in inter-ictal abnormality during sleep. In the "sleep" group the peak times for seizure occurrence are just after falling asleep or just before waking.

Janz notes that absence seizures appear to be more common just after waking although he recognises the problems associated with monitoring attacks by observation alone. He suggests that during sleep actual attacks are rare.

Declerck, Martens, Wauquier and Kums (1982) have attempted to evaluate the changes in spike and wave activity which occur during sleep using either the 24 hour EEG or telemetry apparatus.

In 93% of their patients abnormalities were seen in sleep

stages I and II. During REM sleep generalised regular spike and wave activity tended to be suppressed. In 50% of the patients who showed regular 2.5 to 3.5cps. spike and wave, the spike and wave became polyspike and wave during stages I and II and during stages III and IV it became low frequency paroxysms. Patients with low frequency spike and wave during waking showed similar paroxysms during sleep and in patients with polyspiking this was accentuated in sleep stages I and II.

In some cases of nocturnal seizures, tongue biting, incontinence and headache may be the only sign that a fit has occurred during the night. Davies (1982) reports on two children in whom nocturnal epilepsy was mistaken for a behaviour problem. Both children were drowsy, irritable and inattentive during the day. Both had normal waking EEGs but abnormal sleep EEGs.

Sleep walking and night terrors can be confused with nocturnal epilepsy. Docherty (1981) studied five patients with suspected seizures at night using the 24 hour monitor. One patient showed only an abrupt arousal from stage IV sleep prior to sleep walking, and another showed a sudden transition from REM to wakefulness reporting a nightmare. Such findings would indicate a diagnosis of somnambulism and night terrors and exclude epilepsy.

Jovanovic (1982) discusses 12 patients reporting sleep walking. He used a combination of telemetry and 24 hour

cassette recording and results span 20 years.

Four patients showed epileptiform abnormalities in the EEG. Two showed bilateral temporal spiking just before walking and during it and their behaviour suggested a "psychomotor" form of epilepsy. The other two showed generalised spike and wave discharges during walking only and finally reverted back to stage IV sleep, suggesting a centrencephalic form of epilepsy.

A further 29 patients diagnosed as suffering from somnambulism showed a sudden transition from stage IV sleep to alpha rhythm whilst walking. This was followed by the rapid reoccurrence of deep sleep.

Jovanovic also notes that patients with 'sleep epilepsies' showed most abnormalities in the first part of the night in the descending part of sleep. Patients with 'waking epilepsies' however, tended to show an increase in abnormalities towards the morning around 5 to 7am or just before waking.

A further problem in which epilepsy may be indicated is that of enuresis nocturna. Arunger, Baybas, Gozukirmizi and Zebilci (1978) describe nocturnal enuresis as 'an episodic phenomena accompanying lightening of deep sleepit occurs predominantly during the first cycle of sleep'. In four out of eight of their cases anterior spike and wave activity was seen in sleep stages I and

II but disappeared during REM. In a further two patients rhythmic spike and wave activity was seen in stage I sleep. These abnormalities did not necessarily occur during an enuretic episode. The remaining two patients showed no abnormalities.

Jovanovic however, reports enuresis occurring in adults in stage IV sleep. In children it occurred in all stages though mostly in stage II and least of all in REM. In eleven out of twenty children there was an epileptiform abnormality in the sleep EEG, two during an enuretic episode. He also observed differences in sleep stages between enuretic and normal children. It must be noted however, that in 4% of normal healthy adults and 10% of children whom he studied, Jovanovic found epileptiform abnormalities in the sleep EEG.

Narcolepsy has also been one of the reasons for which patients were referred for 24 hour monitoring. It has been proposed that the sleep of narcoleptic subjects is characterised by sleep onset REM periods (SOREMPs), ie. REM sleep occurring within 15 minutes of sleep onset. Richardson, Carskadon, Flagg, van de Hoed, Dement and Mitler (1978) advocate EEG recording during multiple day time naps in order to confirm the presence of SOREMPs.

Docherty (1981) used ambulatory sleep recording to study two patients with symptoms suggestive of narcolepsy. One of these showed SOREMPs during voluntary day time

naps (in less than eight minutes) and the other simply showed a tendency to oversleep.

The presence of SOREMPs should however be treated with caution as Jovanovic reports a finding of SOREMPs in a normal 60 year old adult. He also found that 8 out of 38 patients with a diagnosis of narcolepsy showed SOREMPs during the following three to four nights.

CHAPTER 3

A STUDY OF 250 AMBULATORY
EEG INVESTIGATIONS

3.1 METHOD

Clinical Investigations

Details of investigations are given in Table 3.1 and 3.2. A total of 250 investigations were carried out on 213 patients. Several 3 channel investigations were repeated if attacks had not been recorded, there were technical problems, the recorded attack was obscured by artifact or if the patient was referred again for an alternative reason.

There were more female patients than male. There were fewer children in the 8 channel group because this recorder was not used in hyperactive children, owing to the high cost of repair should damage occur. The lower age limit was three years in the 8 channel group and 1 year in the 3 channel group. The main reason for this was the lack of space on the scalp for thirteen electrodes and eight pre-amplifiers in very young children and babies. In addition, the 3 channel recorder was lighter and so easily carried by young children, and electrode application and removal was less distressing.

Prior to the purchase of the 8 channel recorder, it was sometimes felt necessary to sacrifice the time/event channel for a fourth EEG channel particularly when partial attacks were suspected and better scalp coverage was required. Thus, 33 recordings were made using 4 EEG

TABLE 3.1

DETAILS OF 3 CHANNEL INVESTIGATIONS

Total patients	163	(37 repeated)
Total males	70	
Total females	93	
Age range	1yr	to 59 yrs
Total under 18 years	81	(49.7%)
Total investigations	200	
4 EEG channels	33	
3 EEG, 1 ECG channel	4	
3 EEG, 1 time/event channel	163	
Total number of days recorded	303	
Mean duration	1.52	± 1.15
Total recordings carried out at home	158	
Total recordings carried out in hospital	40	
Total recordings carried out at home and in hospital	2	

TABLE 3.2

DETAILS OF 8 CHANNEL INVESTIGATIONS

Total patients	50
Total males	17
Total females	33
Age range	3yrs to 54yrs
Total under 18 years	17 (34%)
Total investigations	50
Total number of days recorded	106
Mean duration	2.12 ± 1.6
Total recordings carried out at home	37
Total recordings carried out in hospital	12
Total recordings carried out at home and in hospital	1

channels. This did however, cause problems with the location of events as the event marker consisted of only a brief high amplitude burst of mains interference on EEG channel 4.

Occasionally it was necessary to interchange the fourth time/event channel with an ECG channel when there were possibilities of cardiac arrhythmias being responsible for attacks. Many patients however, had already undergone 24 hour ambulatory ECG recording elsewhere so this was usually not required. The problems of using an ECG channel have been discussed.

The mean duration of recording was slightly longer for the 8 channel investigations as it was preferable to prolong the recording so that an attack could be monitored, rather than the patient returning to the clinic to go through the lengthy procedure of recorder application again at a later date. Three days at least were therefore allowed between each patient.

Most recordings were carried out with the patient remaining in their normal home, work or school environment. Some patients who were in hospital at the time of recording returned home for weekend leave with the recorder still attached.

Table 3.3 shows the number of patients referred for

TABLE 3.3

REFERRING CONSULTANTSINVESTIGATION

<u>CONSULTANT</u>	<u>3 Channel</u>	<u>8 Channel</u>	<u>Total</u>
Psychiatrist	48	8	(22.4%) 56
Pediatrician	60	9	(27.6%) 69
Epileptologist	43	20	(25.2%) 63
Neurologist	25	9	(13.6%) 34
Neurophysiologist	14	2	(6.4%) 16
Physician	10	2	(4.8%) 12

investigation by consultants of different specialities. It can be seen that most referrals came from paediatricians, psychiatrists and epileptologists (the epileptologists being two psychiatrists in our own clinic with a particular interest in epilepsy). This table shows numbers of investigations rather than the number of patients because occasionally the same patient was referred at a later date if the first recording was unhelpful.

Table 3.4 and 3.5 show the reason for which investigations were carried out. Some of the patients were re-investigated for a different reason, for example, if a diagnosis of absence seizures had been made on the first recording, the second recording was carried out to assess the efficacy of anticonvulsant medication. In most cases patients were referred for clarification of the nature of the attack. Patients referred in order to establish localisation in attacks were only recorded using 8 channels as the three channel recorder was felt to provide insufficient scalp coverage to distinguish partial attacks from generalised. Such recordings were used only as a guide to choice of anticonvulsant, none were used as an indication of the site of an epileptogenic focus for surgical candidates.

Patients referred to assess the effect of sleep on the EEG included those with a possible diagnosis of narcolepsy, nocturnal enuresis, night terrors and somnambulism as distinct from epileptic disorder. Several patients were also referred in order to distinguish possible

TABLE 3.4

REASONS FOR REFERRAL FOR 8 CHANNEL INVESTIGATIONS

<u>REFERRAL</u>	<u>NUMBER OF INVESTIGATIONS</u>
? Epilepsy	39
Effect of sleep	3
Clarification of seizure type	8
	<u>50</u>

TABLE 3.5

REASONS FOR REFERRAL FOR 3 CHANNEL INVESTIGATIONS

<u>REFERRAL</u>	<u>NUMBER OF INVESTIGATIONS</u>
? Epilepsy	149
Effect of sleep	16
Monitoring frequency of absence seizures	35
	<u>200</u>

nocturnal seizures from attacks of psychological origin.

Finally, 35 investigations were carried out in order to monitor the frequency of absence seizures. Eight channel recording was found to be unnecessary for monitoring generalised spike and wave activity and it was also a rather lengthy procedure for patients who underwent repeated investigations for assessing the efficacy of anticonvulsant medication. Absence seizures were therefore only monitored using the three channel recorder. In most of these patients the initial diagnosis had been made on the basic EEG or a previous ambulatory EEG.

Patients were also selected on the basis of attack frequency. A requirement of at least one attack per week was made before ambulatory monitoring was carried out using the eight channel recorder. If attacks were less frequent and a longer period of recording was required this was carried out using one of the three 3 channel recorders. This was primarily to ensure maximum effective utilization of the eight channel recorder which was much in demand. Patient selection by other authors has been discussed in Chapter 2.

Apparatus

The equipment used is marketed commercially by Oxford Medical Systems. As yet, no other comparable product is available.

Initially, the study commenced using two recorders consisting of 3 EEG channels and one time/event channel, and one recorder consisting of 4 EEG channels with an event marker (Figure 3.1). The recorder and replay specifications are given in Appendix 2.

The 4 channel recorder

The 4 channel recorder is battery powered, measures 9cm by 13cm and weighs approximately 400 grams. It utilises a standard C120 cassette tape which runs at a speed of 2mm/sec and will therefore last for an average of 24 hours.

The on-head preamplifiers, as described in Chapter 1, have two pin connections with the black lead being indicated by a small embossed circle next to the appropriate pin. A one to two meter lead connects each amplifier to the recorder itself which is worn on the patient's waist. Unfortunately, this junction is rather fragile and if accidentally pulled by the patient the connection to the recorder is broken. As this tended to occur quite often, it was necessary to obtain replacement preamplifiers which could be changed at a moments notice in the clinic.

The 8 channel recorder

The 8 channel recorder (Figure 1.2) consists of 8 recording channels and a permanent ninth channel on which a time and event code is recorded. The recorder is slightly larger than the 3 channel (16cm by 12cm) and weighs

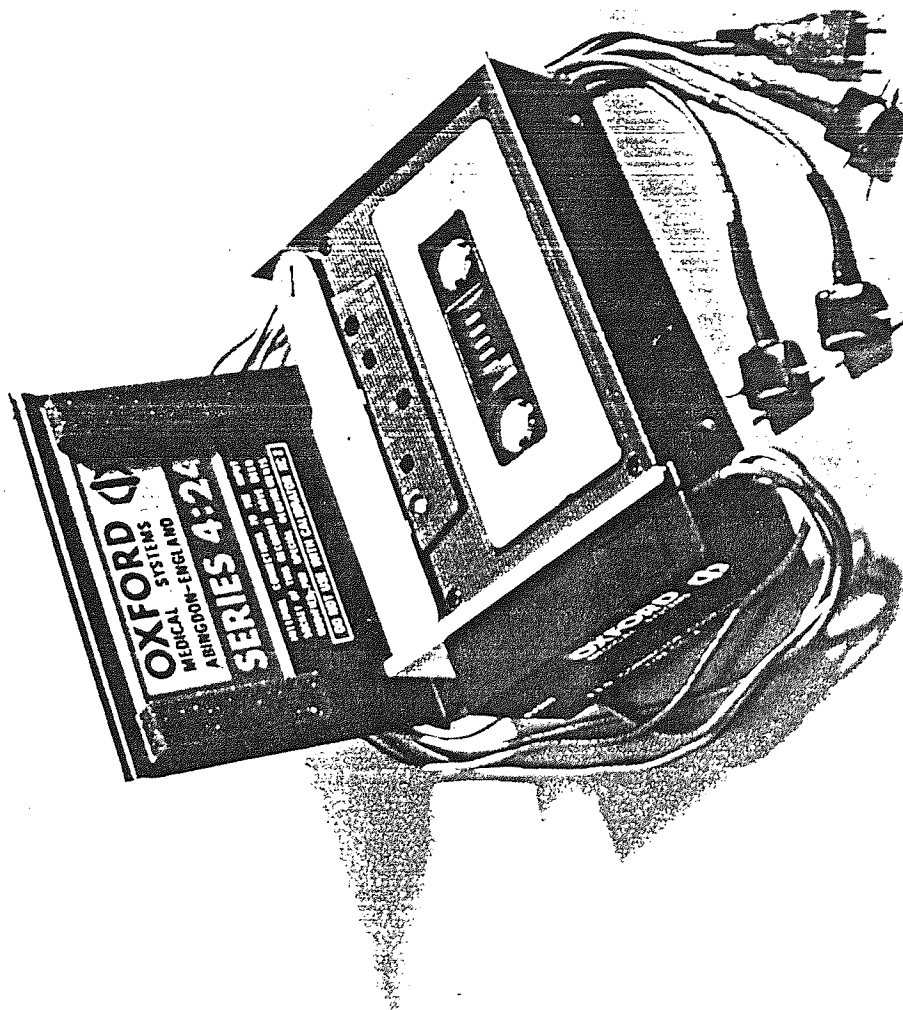


FIGURE 3.1 4 CHANNEL RECORDER

700 grams. Dual-ended electrodes are used to link each electrode with two channels and produce traditional bipolar montages. The recorder has its own digital clock which greatly increases the accuracy of the timing of events.

Recording Electrodes

Ten millimetre silver/silver chloride electrodes were used with short 5cm leads to ensure minimum lead movement artifact and reduced interference from external noise. Ten recordings were also carried out with at least one recording channel consisting of tin electrodes. As these electrodes do not require chloriding it was thought that they would save considerable time. They were therefore evaluated in comparison with the silver/silver chloride electrodes and the results are given in Section 3.2.

Collodion glue was used to attach the electrodes and preamplifiers to the scalp. This forms a non-toxic plastic skin which is later dissolved using acetone.

Neptic gel was used as the electrolytic interface and consists of a mixture of glycerine and sodium chloride. No untoward reactions were noted from the neptic gel, collodion or acetone.

The 4 channel replay system (P.M.D.12)

The 4 channel playback system is shown in Figure 1.1. It consists of a twelve inch black and white monitor screen which is connected to a top loading cassette replay system. Tapes may be replayed at twenty or sixty times real time, displaying either an 8 or 16 second page at a time. All three (or four) channels can be displayed, or 64 seconds of any single channel can be viewed. The EEG can be stopped and back-paged by 16 seconds for closer examination.

There is a choice of 0.1 or 0.3 second time constants but the high frequency filter is fixed at 40Hz.

A cursor is displayed on the screen showing a 100uV calibration signal at one second intervals. This can be moved up and down and from side to side on the screen. The gains on all four channels are individually adjustable.

If the fourth channel of the recorder has been used as a time/event channel the tape is rewound and the time at which recording commenced is entered into the replay deck. The time on tape is then shown on the deck and is accurate to within one minute. It is also possible to stop the playback automatically on the page at which the event button was pressed. If no time code was recorded on the tape, for example if the fourth channel was used for ECG, then the replay deck estimates the time from the number of

revolutions of the reel. This method however, was found to be very inaccurate especially if the tape had been frequently stopped and rewound.

The 8 channel replay system

This system (Figure 1.2) has all the facilities of the 3 channel replay, but several have been updated and several added. The time on tape is accurate to within one second and the point at which the event button has been pressed is visible on the cursor. There is an additional replay speed of 40 times real time and a wider range of high and low frequency filters. It is possible to scan 32 seconds of EEG in real time in either direction and so significant events are more easily examined.

Audio replay

Both playback systems enable the user to listen to the frequencies arising from any particular channel. Certain artefacts such as chewing have characteristic sounds which are distinct from the frequencies heard in conjunction with genuine abnormalities. The sound is heard several seconds prior to the visual EEG and thus helps the user to stop the tape at a significance place more easily when replaying at higher speeds.

Obtaining a print-out from the tape

Both replay systems have a writing out facility, either in

real time or at high speeds. A signal is taken to a standard EEG machine head box (Nihon Kohden 16 channel) and the gains reduced to 100 μ V per 12.5mm pen deflection. To avoid double filtration of the signal the high frequency filters on the EEG machine must be kept to a minimum.

High speed write out requires an EEG paper speed of at least 600mm/sec to obtain a 30mm/sec paper record. Unfortunately, the frequency response of normal pen recorders is insufficient to reproduce the desired waveform and an ink jet EEG machine is therefore required. A compressed print-out however, is obtainable at reduced paper speeds and some EEG abnormalities, such as spike and wave activity, can be recognised from normal background activity since they are often of higher amplitude. Other authors (Ives and Woods 1975) have used this method to analyse spike and wave activity over a 24 hour period. However, it is often difficult to distinguish between genuine abnormality, artefact and sleep rhythms.

Procedure

All patients received a letter containing a description of the investigation (Appendix 3). Clinics were carried out on Mondays and Thursdays and thus a minimum of 3 days was allowed for each investigation.

Prior to the patient's arrival, the recorder was calibrated for at least 20 minutes using a 100uV square wave at 1 second intervals. A monitor box ensured that all channels were functioning, or the calibration signal could be written out from the recorder onto the EEG machine. Unfortunately, this method did not ensure that the signal was actually being recorded onto the tape but simply tested the functioning of the preamplifiers.

The basic EEG

Several early ambulatory recordings suggested a possible EEG asymmetry which required clarification by a basic EEG. Some of these arose from faults within the recorder itself, two of which can be seen in Section 3.2.

Additionally, in the early stages of recording montage design was very speculative, some of the configurations used originally are shown in Figure 3.2. It was therefore decided that a basic EEG should always be carried out prior to the ambulatory EEG so that ambulatory EEG electrodes could be applied over areas of abnormality. Thus, most of the basic EEGs were carried out in our own laboratory either on the same day or within a few days of the 24 hour EEG. In a small percentage of patients either the EEG itself, or an EEG report was obtained from another EEG department.

On arrival at the laboratory the whole procedure was explained to the patient and he or she was made to feel

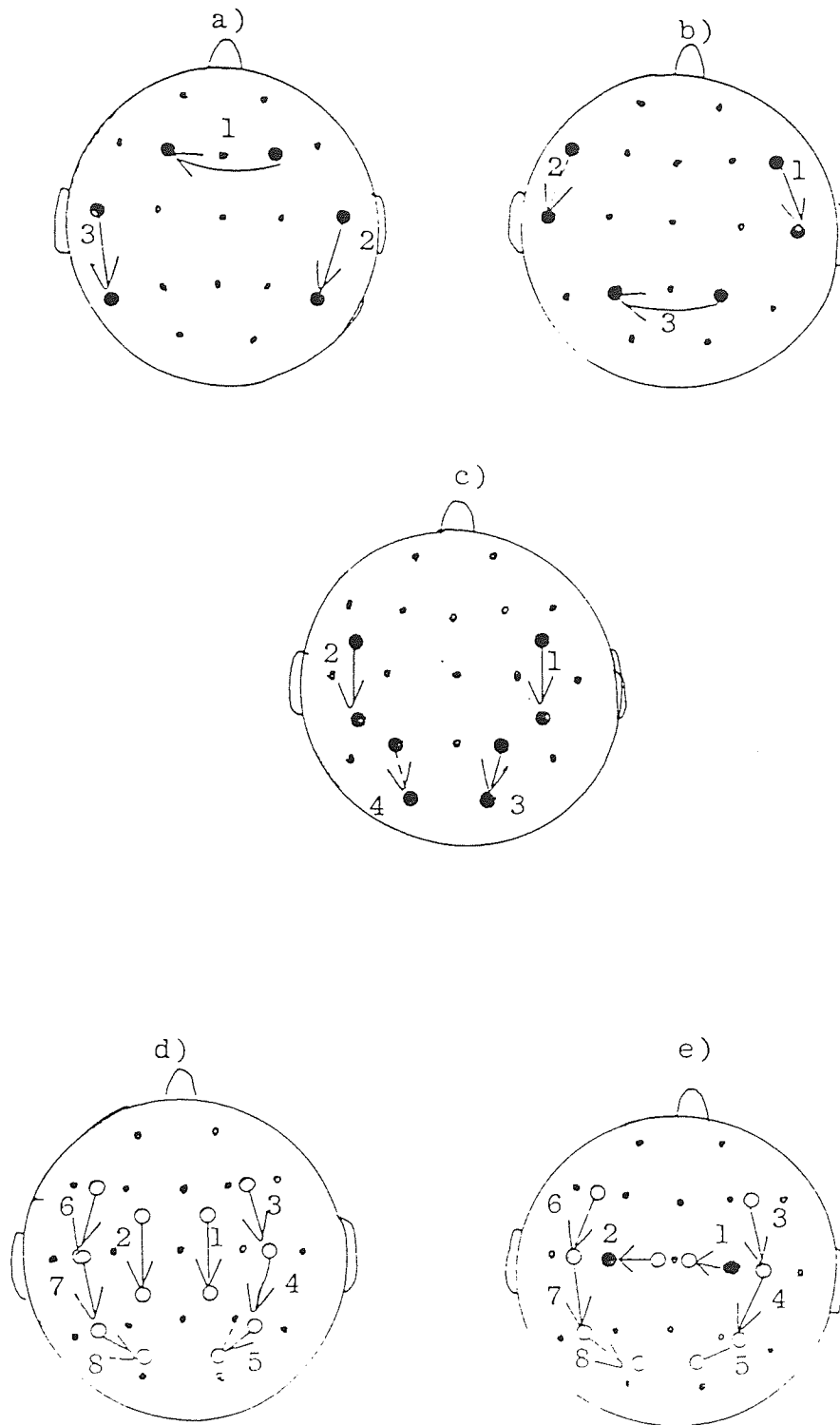


FIGURE 3.2 EXPERIMENTAL MONTAGES AND MONTAGES IN PRESENT USE

- a) 1 & 2 recorded too much muscle, 1 was often attenuated therefore, not good for recording anterior abnormalities
- b) 1 & 2 recorded too much eye movement and was cosmetically unacceptable. 3 recorded alpha but did not help lateralisation if this was unclear in 1 and 2
- c)d)e) Montages in present usage

as comfortable as possible. The basic record was carried out using the standard procedure for the Clinical Neurophysiology Unit. The recordings were made on a fourteen or sixteen channel Nihon Kohden machine. Bipolar recording was used, unless the patient showed a focal abnormality in which case average reference recording was also carried out. Patients were asked to lie on a bed during recording.

Hyperventilation was performed on a parasagittal bitemporal montage, patients were asked to overbreathe for a minimum of three minutes which included a period of eye closure. Subsequently, a transverse montage was used, again including testing with the eyes closed. Patients were screened for photosensitivity using a Grass PS22 photic stimulator at intensity 2. Jeavons and Harding (1975) have shown that some patients exhibit increased photosensitivity with pattern, therefore a grid was placed over the strobe lamp. Frequencies between one and sixty flashes per second were delivered each being presented for five seconds with eyes open and five seconds with eyes closed as Jeavons and Harding (1975) have shown that some patients are more sensitive at the time of eye closure. This procedure was carried out on a bitemporal, parasagittal montage.

If any abnormality was detected in the basic EEG the ambulatory EEG electrodes were positioned over the area of maximum abnormality.

Attaching the ambulatory EEG equipment

Once the montage had been chosen, the electrodes were applied using collodion glue. These were positioned so that the ends were pointing in an upward direction to allow the preamplifiers to be fitted in between each pair. Hair clips were used to keep the hair back whilst applying. The electrodes were then gelled so that resistances of approximately 5 to 10Kohms were achieved. The holes in the electrode cups were then glued over to prevent the gel drying out during the twenty-four hours.

The preamplifiers were then plugged into the electrodes. The earth lead was attached to two electrodes positioned in parallel on the scalp, usually around the rolandic region or where the patient had sufficient hair to hide them. The manufacturers had recommended that the earth lead could be placed on the back of the head, close to the nape of the neck. It was found however, that this position caused the earth lead to become detached due to head and neck movement.

Before glueing the preamplifiers to the scalp the recording was checked for signs of artefact. The same interface which had previously been used to record the calibration signal onto the EEG machine was again used to monitor the background EEG. If the recording was artefact free, the preamplifiers were then glued down by parting the hair and placing a small amount of glue on the scalp underneath each one. Special attention was paid to the earth lead

since if both electrodes became detached the tape recording would be blank. One earth electrode however, would maintain the recording if the other was lost. The connections between electrodes and preamplifiers were also glued over to keep them in position. It was a general rule that amplifiers were only glued down sufficiently if, when they were moved, the scalp moved with them without any play. The hair was then removed from the hair clips and brought down to cover over the preamplifiers and electrodes. When necessary, the hair was actually glued over the preamplifiers. The leads were then fed towards the nape of the neck and glued into position beneath the hair. The recorder was fed beneath the patient's shirt or jumper so that the leads were invisible. Blenderm tape was used to attach the wires to the patient's back to keep them out of the way.

Before completing the procedure, the patient was asked to shake his head from side to side, nod up and down, close his eyes and pretend to chew. These artefacts can be seen in Section 3.2. This enabled comparisons to be made at a later date should spurious abnormalities appear on the tape. It also ensured that a loose connection would not appear should the patient perform any vigorous head movements over the course of the day.

The recorder was placed in a small leather pouch and put on a belt around the patient's waist or over his shoulder on a shoulder strap. Most patients found

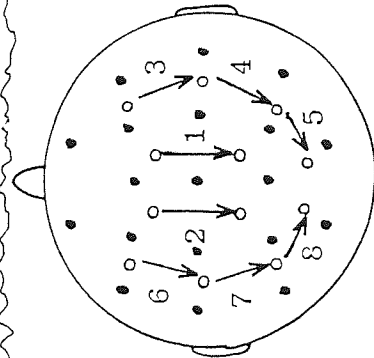
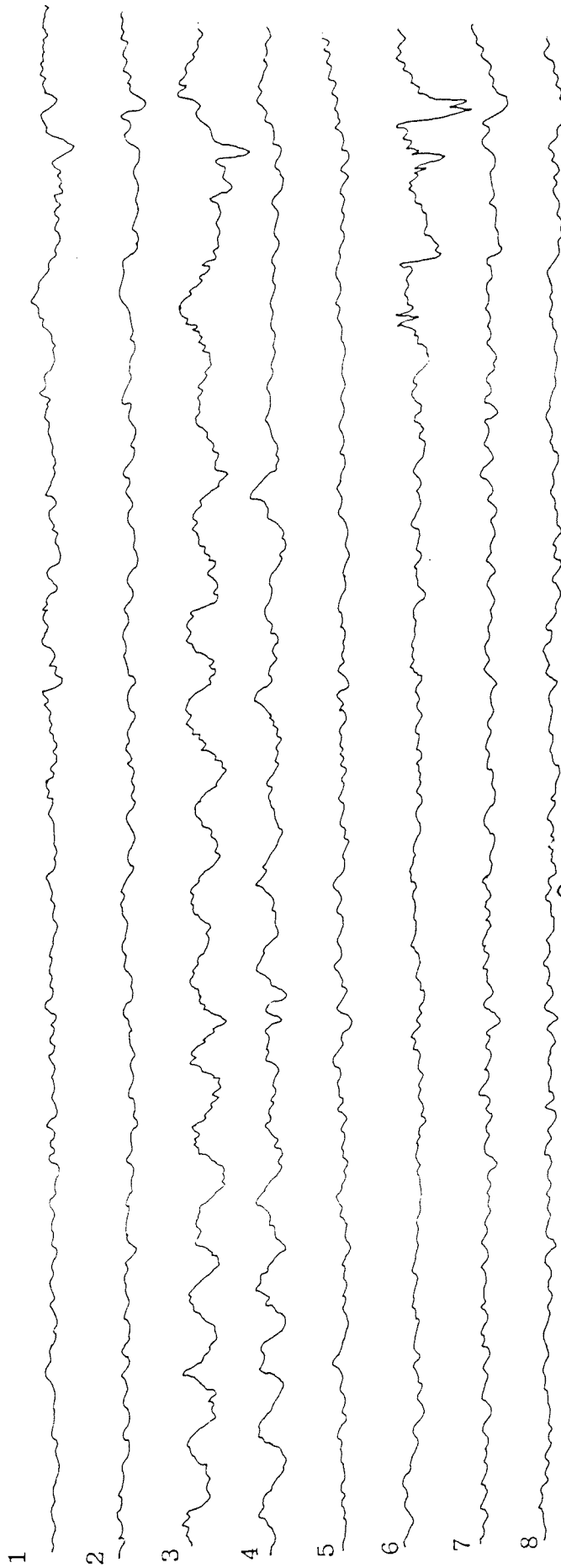
the belt more comfortable as there was no weight over the shoulder and the recorder did not swing forward when the patient leaned forward or bent down. For added security in some children, both belt and shoulder strap were used. If it was suspected that the patient might interfere with the recording, the recorder was taped around with blendern before being placed in the leather pouch. Some patients preferred to wear a hat or a scarf around their necks to hide the leads.

An instruction sheet was given to all patients, if possible in the presence also of another adult, (Appendix 4) explaining that care should be taken with the equipment when hair combing or carrying out any activity which might involve damaging the preamplifiers. They were told not to bathe or shower and to tape the wires low down their back at night to prevent wires becoming entangled around the neck. Special attention was given to this with very young children or persons who were likely to experience attacks at night. Patients were told either to place the recorder under their pillow, or to leave it on their waist if they felt they were likely to get up in the night and forget they were wearing it. This was important in patients with possible "sleep-walking" attacks.

Patients were also instructed to press the event button at the time of a possible attack and to inform persons with whom they were spending the day to press the button if necessary.

A diary sheet was given to all patients to be filled in at fifteen minute intervals (Appendix 5). It consisted of two columns one of which was to be filled in with daily activities, including anything which might interfere with the recording, and the other to be used for descriptions of attacks. Patients were asked to fill in the time that the attack occurred, the time the button was pressed and to give as accurate an account as possible of the attack itself. Quite often a relative provided this account and this was extremely important for distinguishing genuine abnormality from artefact. Figure 3.3 shows the EEG during an attack in which the patient felt a pain in her head and rubbed her right temple. A similar artefact was reproduced in the laboratory when the patient was asked to mimick an attack. Figure 3.4 shows an attack which occurred at night during which the patient tossed his head rhythmically from side to side punching his forehead with his right fist. Although this recording is more obviously artefactual, a similar artefact was later produced in the laboratory.

Patients were always instructed to return to the laboratory the following day whether or not an attack had been recorded. This was to ensure that all of the apparatus was functioning correctly. If an attack had been recorded the tape was examined using the replay system to ensure that the attack was adequately marked by the pressing of the event button and that it was not obscured by artefact. It was also important to clarify whether a typical attack had been recorded as some patients complained



100uV
1 SEC.

N.G. AGED 46.

FIGURE 3.3 PATIENT RUBBING RIGHT TEMPLE DURING SIMULATED ATTACK

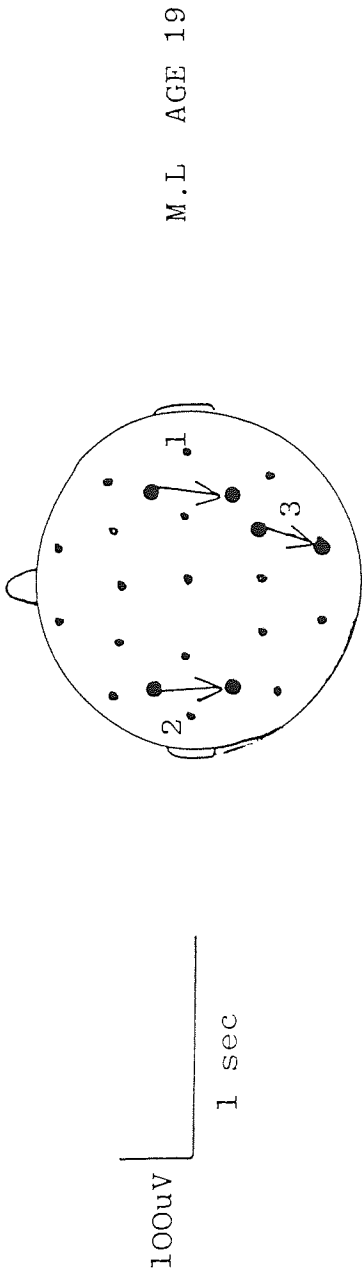
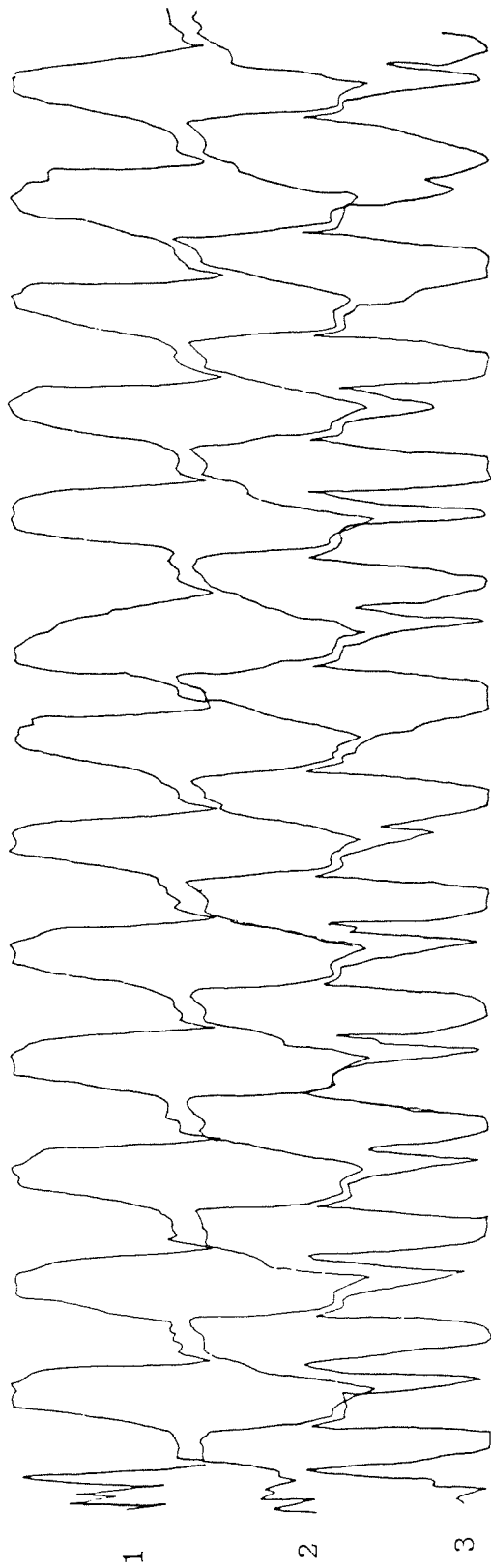


FIGURE 3.4 PATIENT TOSSING HIS HEAD RHYTHMICALLY AND PUNCHING HIS FOREHEAD DURING ATTACK

of various symptoms. Having recorded a satisfactory event, the apparatus was removed. If it was necessary to continue recording, patients were given sufficient tapes and batteries to last for a further two days and also taught how to re-gel electrodes and change tapes. They were also given a set of written instructions to follow, those for the 8 channel recorder are shown in Appendix 6. If the patient lived alone or it was suspected that they could not be relied upon to continue the recording themselves, they were asked to return to the clinic every day.

Recorder removal

The electrodes and preamplifiers were removed using acetone. The patients clothing was protected by placing sheets of soft paper towel around the neck and the head was tipped back to prevent acetone running into the eyes. Ample amounts of acetone were used so that the equipment easily became loose and was not pulled. This was carried out as quickly and efficiently as possible, particularly in children who sometimes found recorder removal distressing. Once the apparatus had been removed the hair was combed through with a metal comb using more acetone. Patients were instructed to shampoo their hair several times and then to use conditioner as this eases combing and counteracts the slight drying effect of the acetone.

Collating the recording

As several recordings were carried out each week it was

necessary to ensure that tapes did not become confused and that each tape was used a maximum of only six times. Therefore, each tape was numbered on the cassette itself and on the cassette case. The number was also written at the top of the patient's diary sheet and the patient's name and the date was written in the space provided on the cassette case.

Tapes on which attacks were recorded were kept separately from re-usable or new tapes. Each tape, whether previously used or not, was cleaned prior to recording using a bulk eraser. In order to ensure that a large D.C. potential had not been put on the tape by incorrect cleaning, a portion was replayed on the P.M.D. 12 and then rewound ready to be used. Both recorder and playback tape recording heads were cleaned periodically.

Replaying and reporting tapes

The entire tape was examined by the author. If several days had been recorded but only one included an attack, that tape only was examined unless it was found necessary to refer to other days to clarify background abnormalities. Similarly, if several days had been recorded without the occurrence of an attack, one day only was examined in its entirety.

At the beginning of the tape, replay was carried out at 20 times real time using an 8 second page. This was to 'acclimatise' oneself to the background EEG. After

approximately two hours of recording the replay speed was increased to 40 or 60 times real time with a 16 second page. Usually an artefact free channel or one that was most likely to show abnormality was chosen for listening. With either replay system this was usually one of the mid-temporal channels. At sleep onset the tape was again slowed and examined more closely until the end of the first rapid eye movement (REM) sleep period. The replay speed was increased until just before waking and then slowed again for closer inspection. The rest of the tape was examined at faster speeds. Obviously this procedure varied slightly from patient to patient depending on the background EEG. Any one record could therefore take between 30 and 90 minutes to analyse.

On the eight channel replay, attacks were scrolled in real time. On the three channel system however, they had to be examined page by page. The time constant used on both machines was 0.3 secs. On the 8 channel replay a 30Hz filter was preferred since the 15Hz filter tended to round off muscle spikes so that they appeared as sharp waves.

If several attacks had been recorded and they were unclear or showed some variation, they were often written out on the EEG machine so that direct comparison was possible between each one. Similarly, if background abnormalities occurred at varying intervals throughout the tape and the morphology of these varied, they were also written out.

Comments concerning possible abnormalities, artefacts and descriptions of the EEG during attacks were written on the diary sheet for later examination by Professor Jeavons or Professor Harding. The basic EEG was reported as well as the ambulatory EEG if it had been carried out on the same day.

A standard report can be seen in Appendix 7. This usually consisted of a description of the montage used, the duration of the recording and a clinical description of any attacks together with the EEG findings. If abnormalities were found which were not present in the basic EEG these were also reported on as well as any abnormalities present during sleep. Reports were then sent back to the referring consultant.

Artefacts encountered during ambulatory recording

In order to catalogue possible artefacts and perfect the recording technique, 3 normal subjects were recorded prior to any patients. The montage was an early one which is now no longer used. Some artefacts which were recorded from patients are also included in this section.

Figures 3.5 and 3.6 show artefacts which arise from the recorder. In Figure 3.5 one electrode has become detached and a pseudo alpha rhythm is seen. In Figure 3.6 the amplifier from channel 2 is hanging loose and yet the trace still shows what appears to be background EEG activity.

Figures 3.7 and 3.8 illustrate the kind of artefacts produced if the amplifier leads are pulled or the electrodes are touched. The latter is more obviously artefactual although the variation in polarity makes the sharp waves in figure 3.7 unlikely to be genuine abnormality.

Head nodding and shaking are carried out in the laboratory before the patient leaves, (Figures 3.9 and 3.10). If the actions are very vigorous the muscle activity seems to be obliterated and slow activity is seen, which appear very similar to genuine abnormalities seen

in some partial seizures. In general however, the slow activity tends to begin and end abruptly and there is no slowing of the frequency towards the end of the episode.

Figures 3.11 to 3.13 show how body movement can cause large D.C. drifts in the EEG which intersperse with sharper elements due to interference with the electrodes. Note how the background EEG in channel 1 tends to appear attenuated, possibly due to the use of trans-hemispheric recording causing equipotentiality.

Figure 3.14 shows the effect of static on the EEG produced by the subject putting his head next to the T.V. screen. A similar artefact, which obliterated all channels, was seen in one patient when returning to the clinic in an ambulance as the driverspoke into his radio.

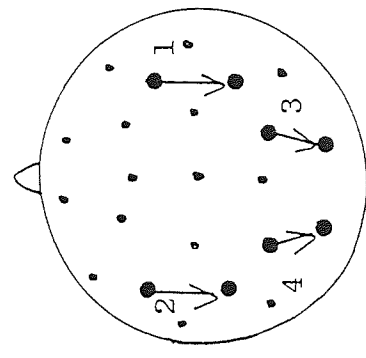
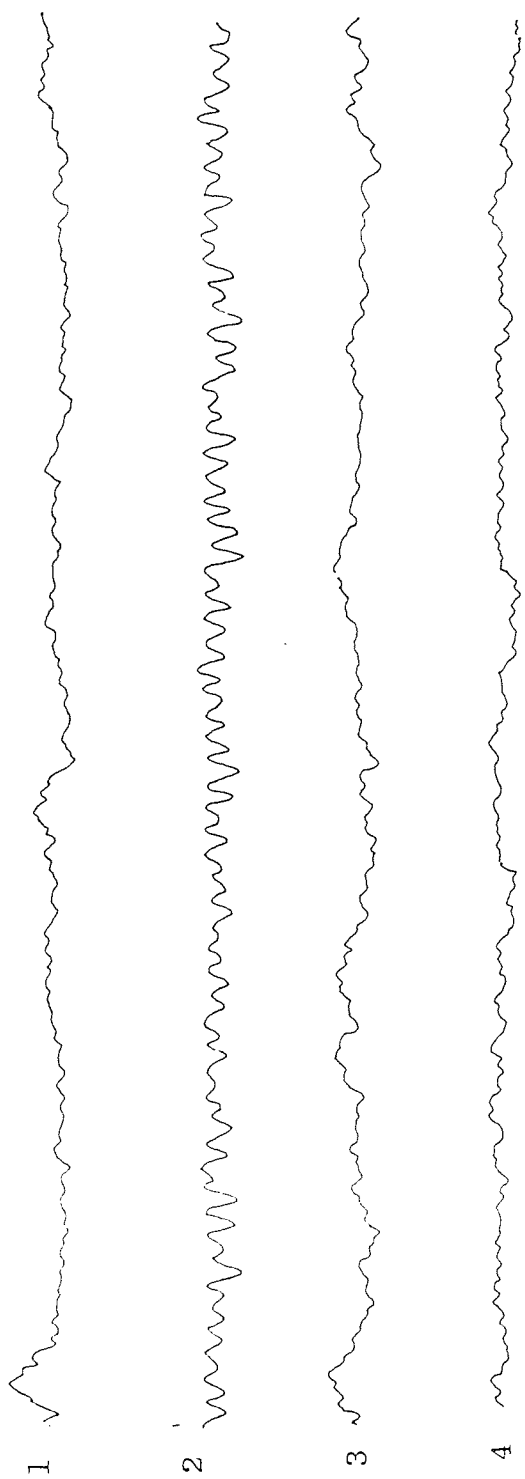
Figure 3.15 is chewing artefact which is easily differentiated by sound. This produces more high frequency components which easily differentiate it from spike and wave activity both by sound and visually.

Eye movements are seen in Figure 3.16 and 3.17. These are usually easily differentiated from genuine abnormality due to their distribution.

Tooth-brushing is seen in Figure 3.18 from a normal subject, and in 3.19, from a patient. In Figure 3.18

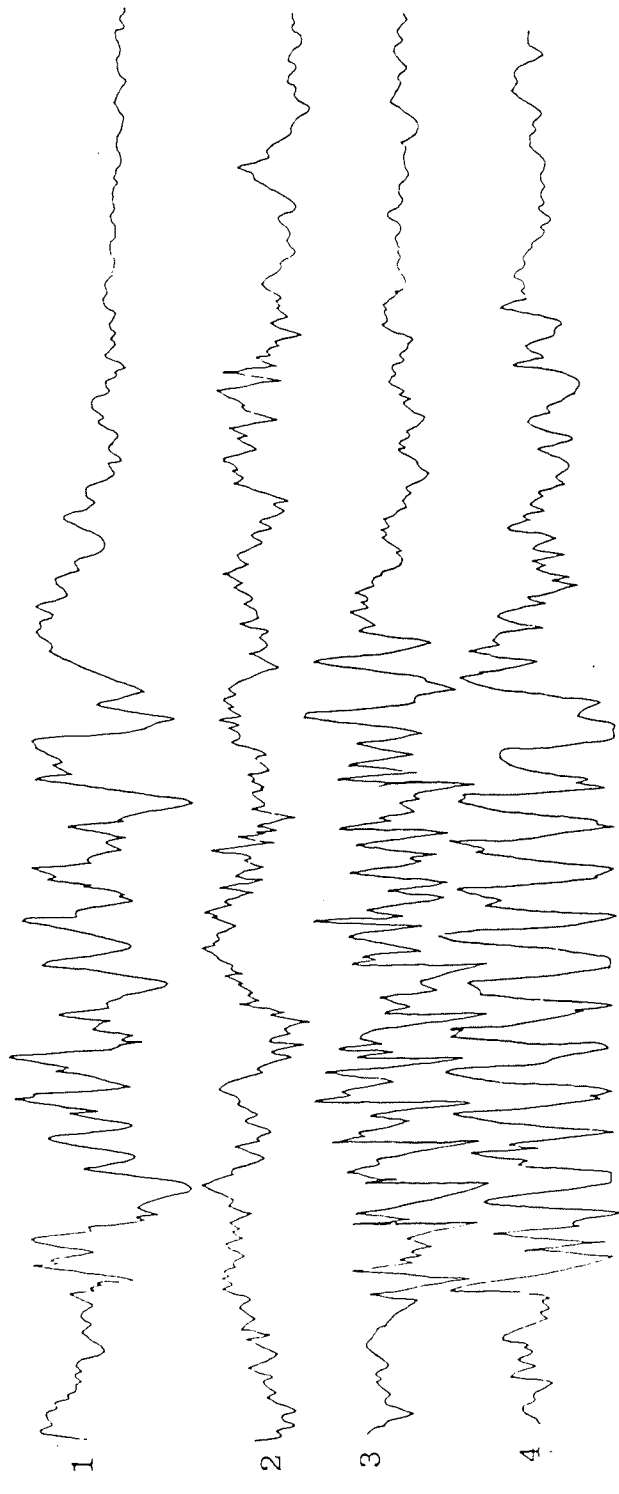
it appears asymmetrical whereas in 3.19 it appears bilaterally and extends slightly into the central regions. Typically, sporadic bursts similar to this are seen for a few seconds prior to sleep and just after waking.

Walking and running artefact are seen in Figures 3.20 and 3.21. The patient shown had a particularly sprightly walk. Note how artefact is maximal in temporal regions but is seen to a lesser extent in central regions. These central channels often prove of value when movement artefact obscures temporal channels during attacks. There is striking similarity between running artefact and polyspike and wave activity. In such instances the diary sheet is of particular value.

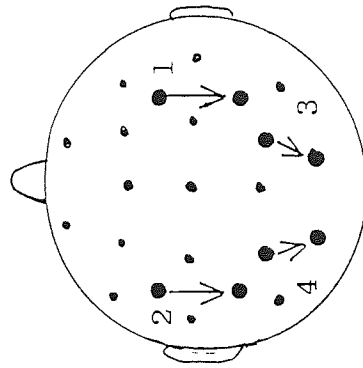


100uV
1 sec

FIGURE 3.5 ONE ELECTRODE DISCONNECTED, CREATING 10 c.p.s. ACTIVITY



100uV
 1 sec



D.B AGE 10

FIGURE 3.6 IRREGULAR BURST OF SPIKE AND WAVE ACTIVITY WITH CHANNEL 2 AMPLIFIER NOT ATTACHED

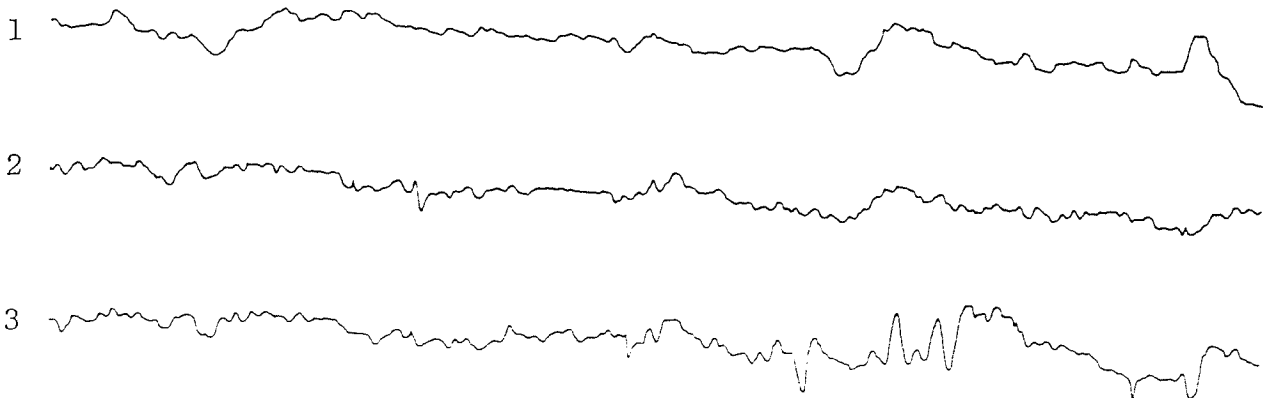


FIGURE 3.7 LEAD PULLING

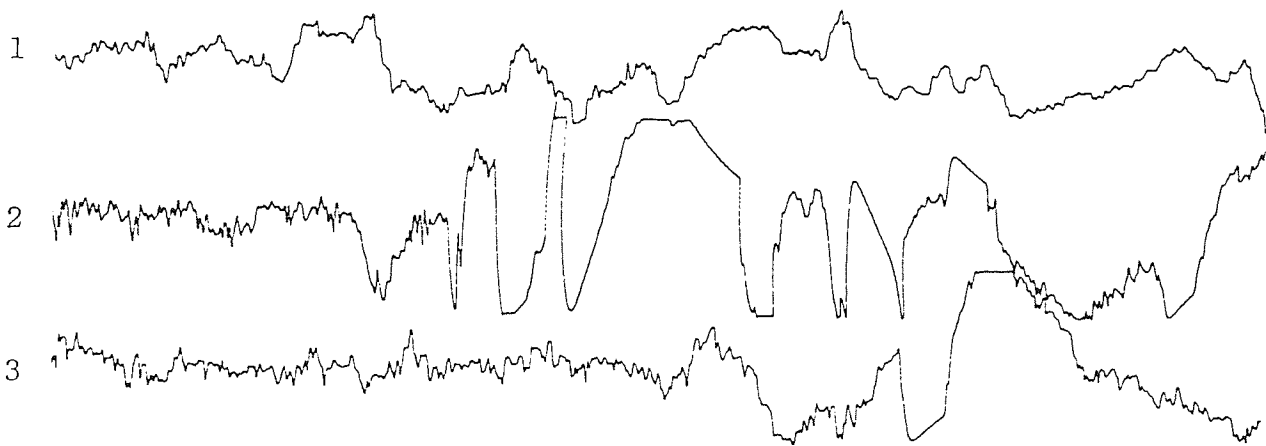
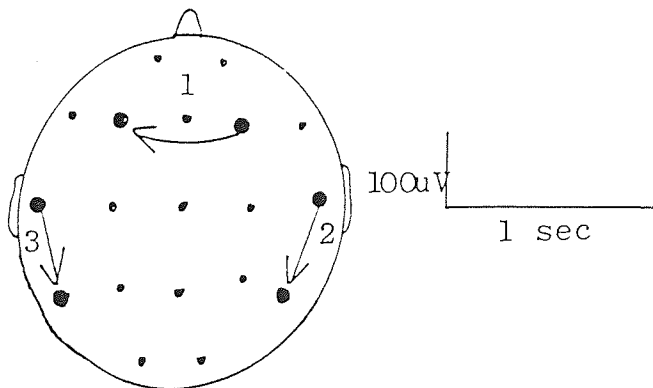


FIGURE 3.8 TOUCHING ELECTRODES



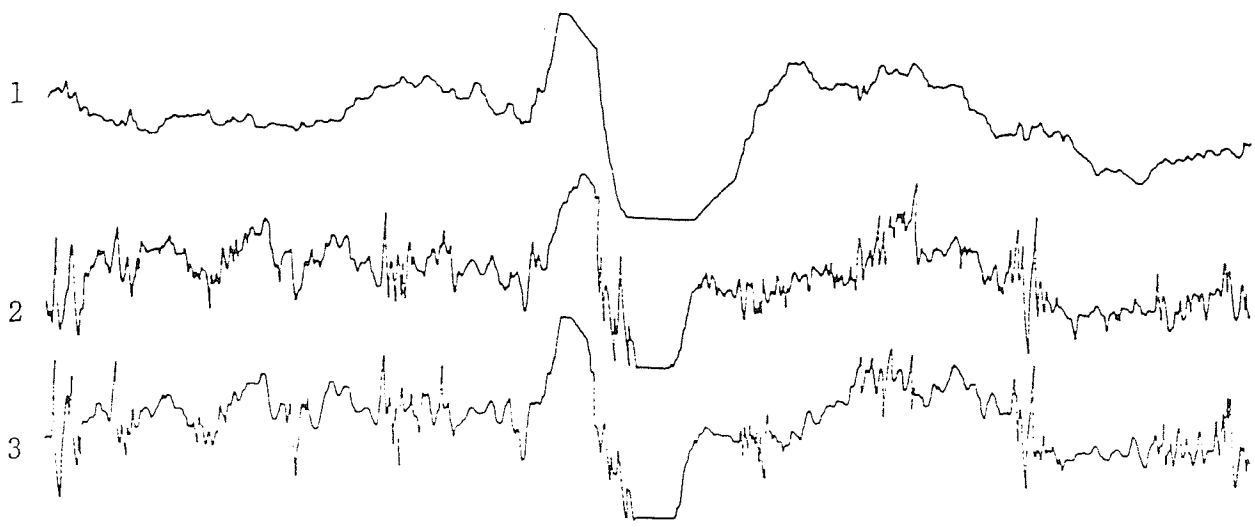


FIGURE 3.9 NODDING

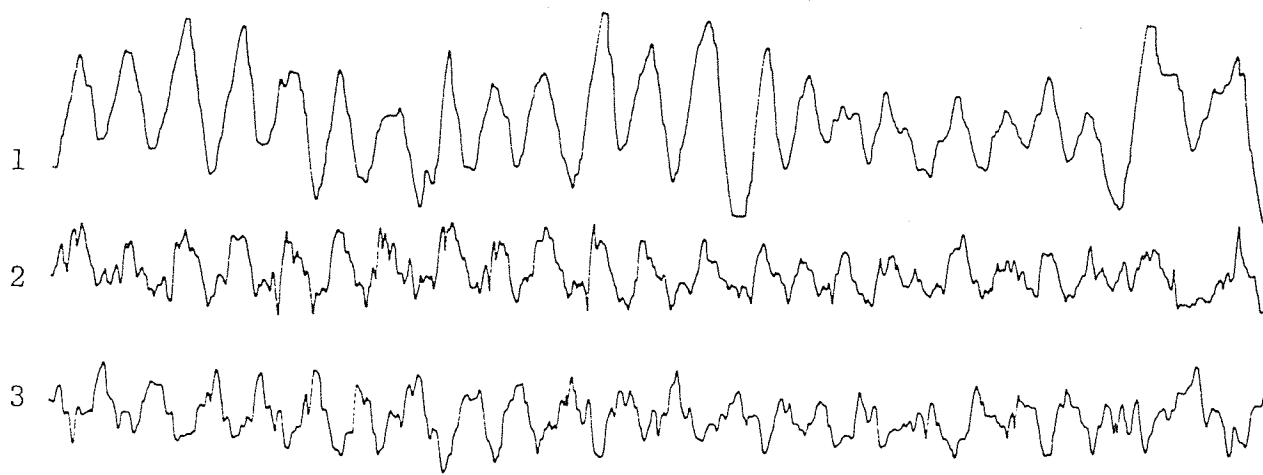
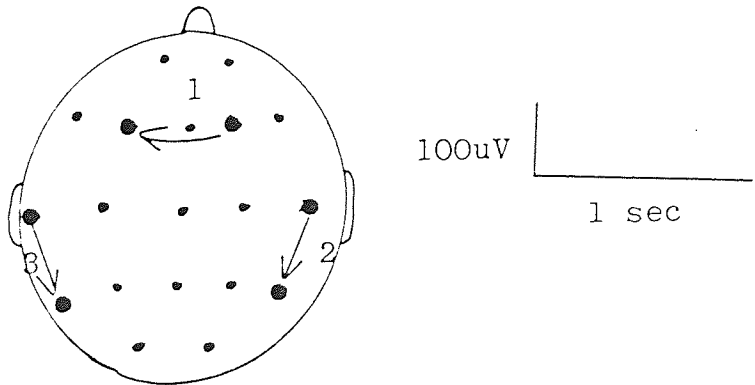


FIGURE 3.10 HEAD SHAKING



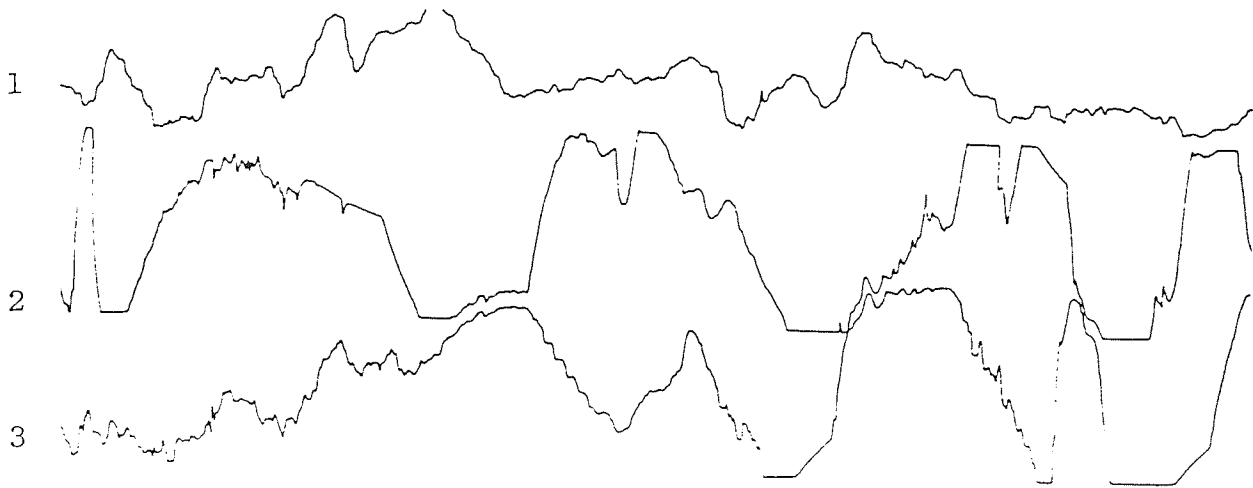


FIGURE 3.11 TURNING OVER IN BED

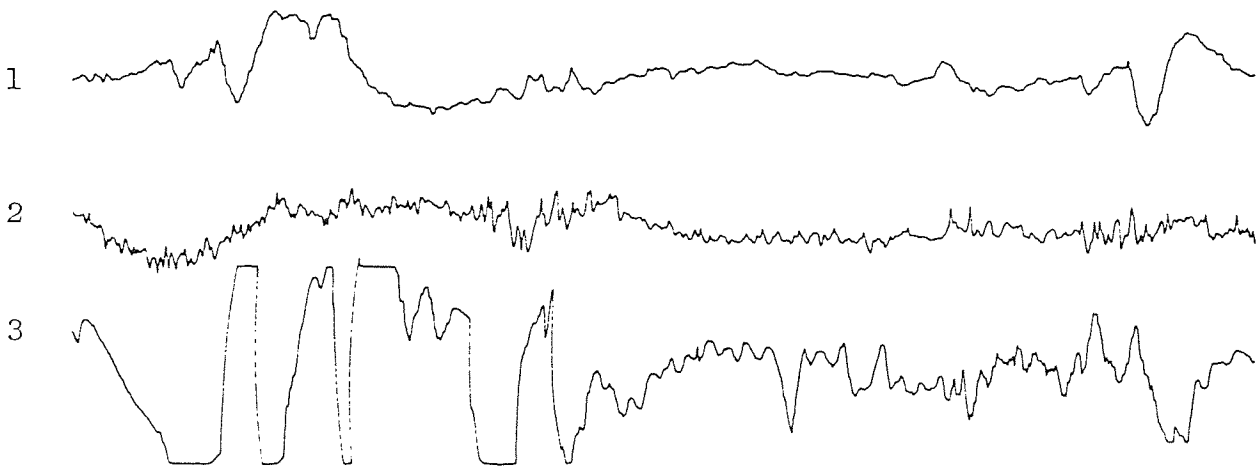
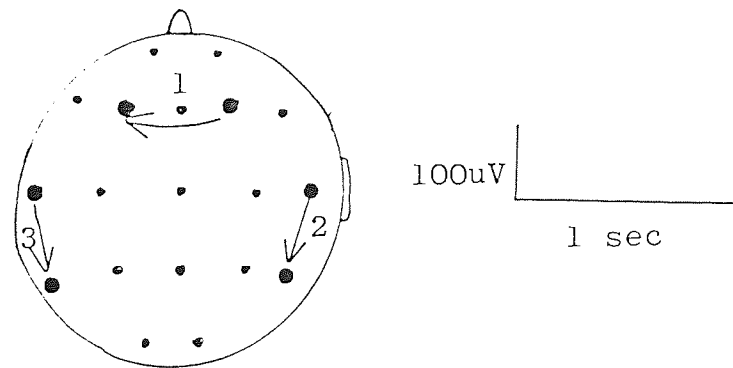


FIGURE 3.12 UNDRRESSING



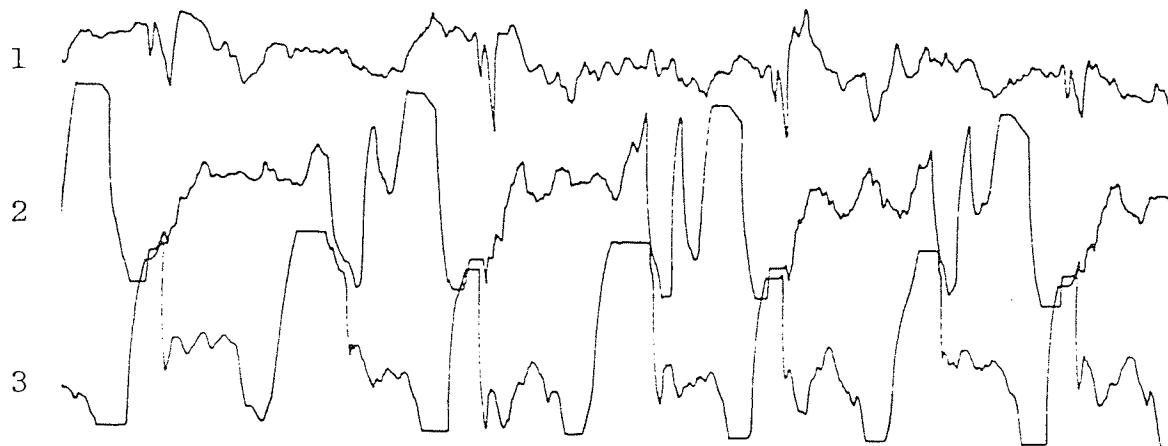


FIGURE 3.13 CHILD ROCKING (PATIENT)

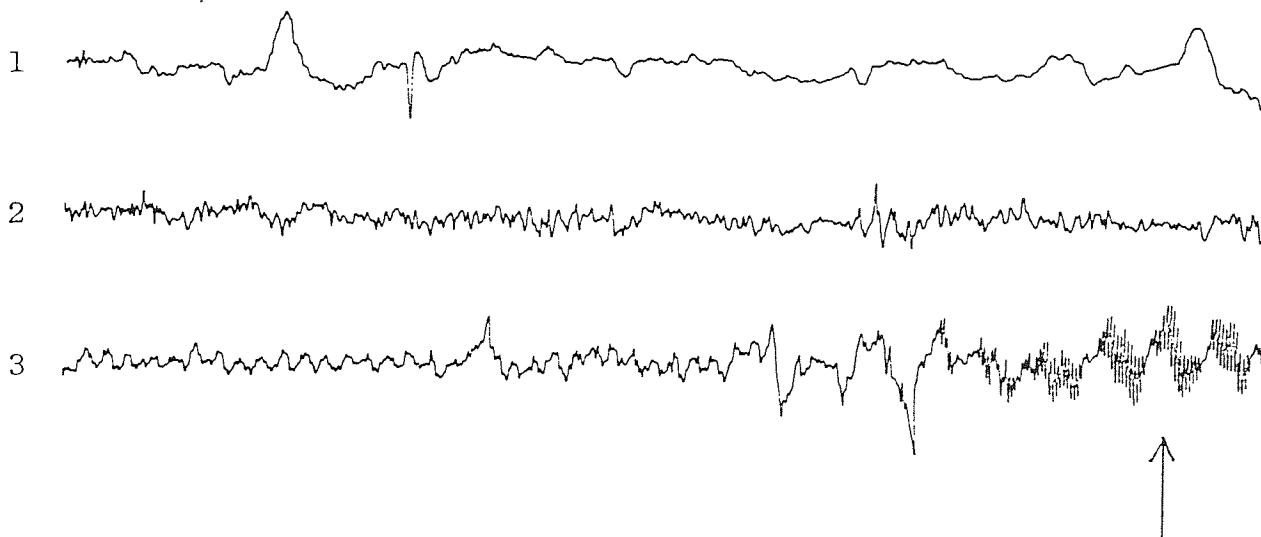
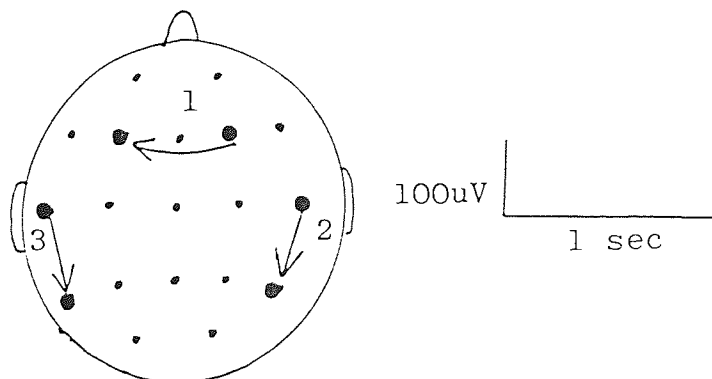


FIGURE 3.14 STATIC



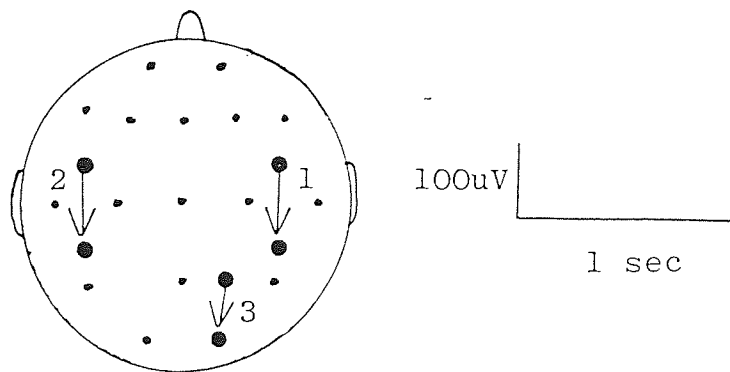
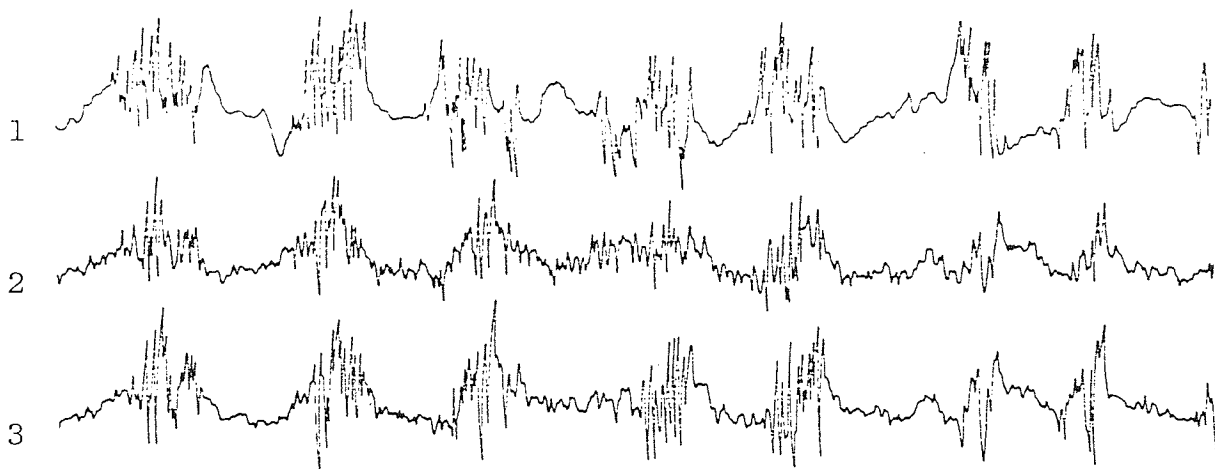


FIGURE 3.15 CHEWING

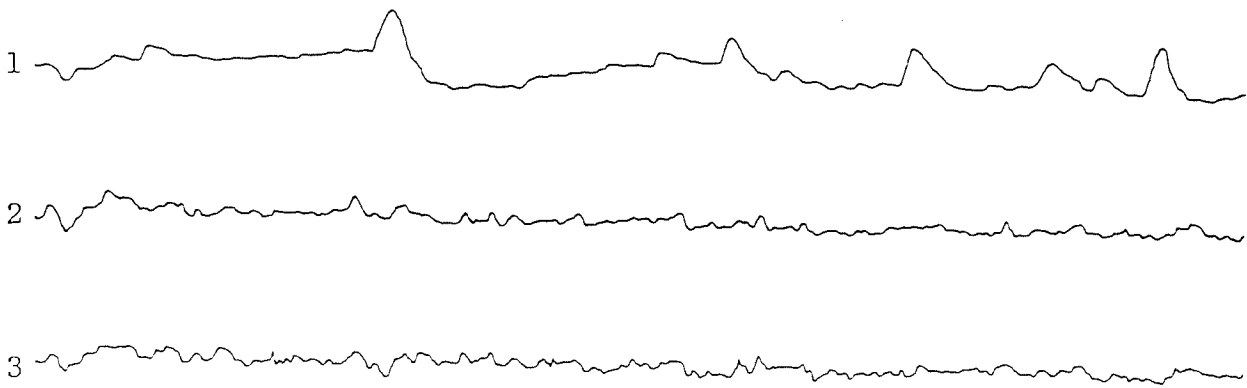


FIGURE 3.16 SPONTANEOUS EYE MOVEMENTS

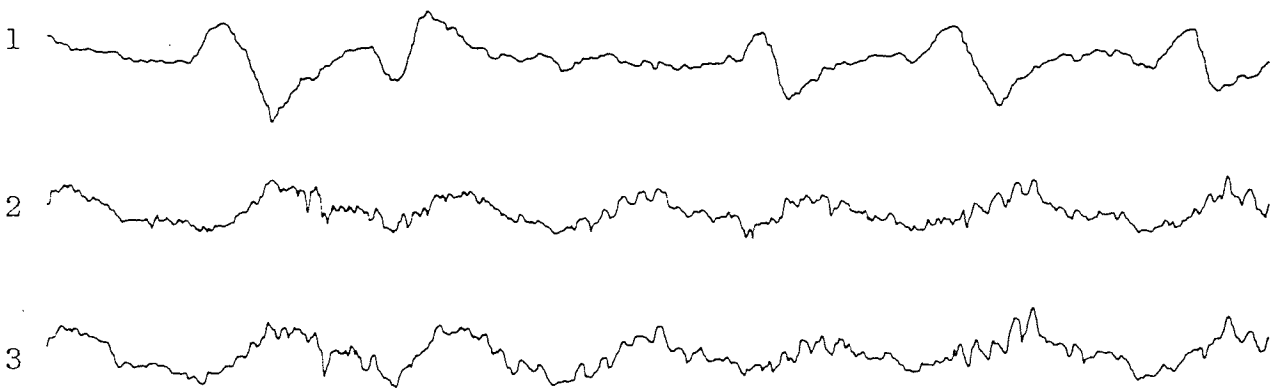
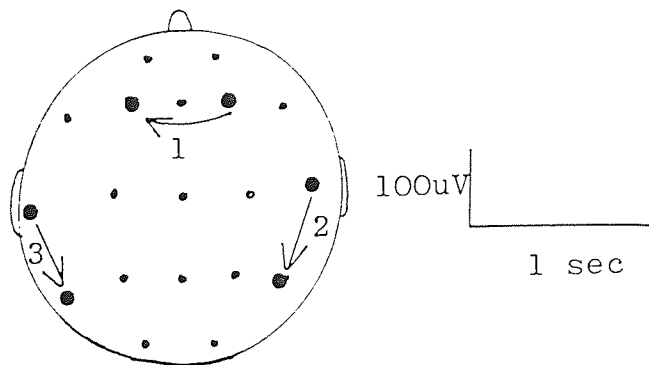


FIGURE 3.17 BLINKING



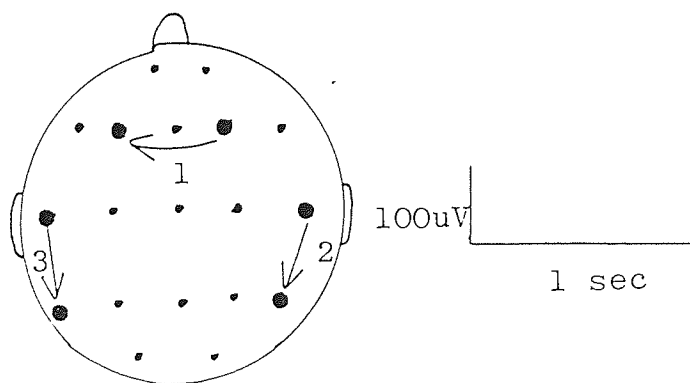
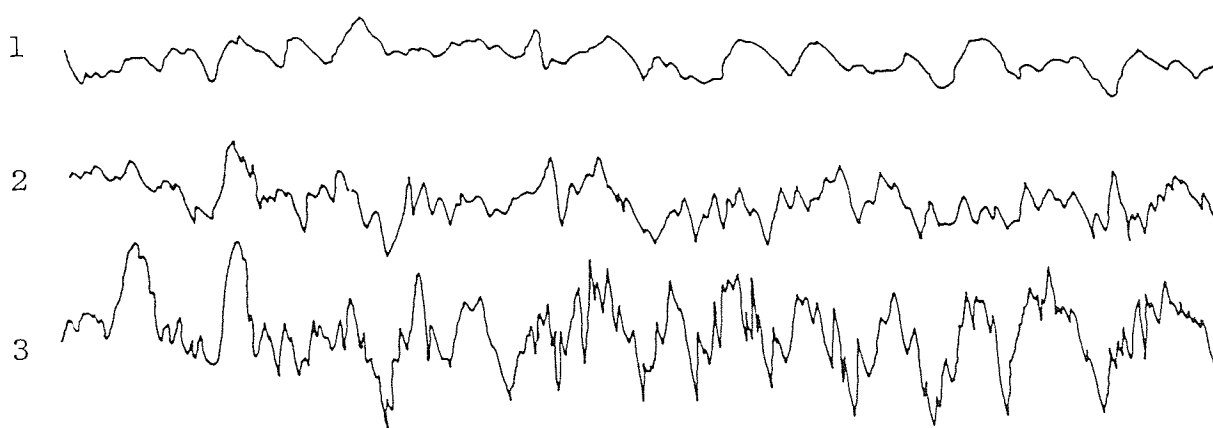
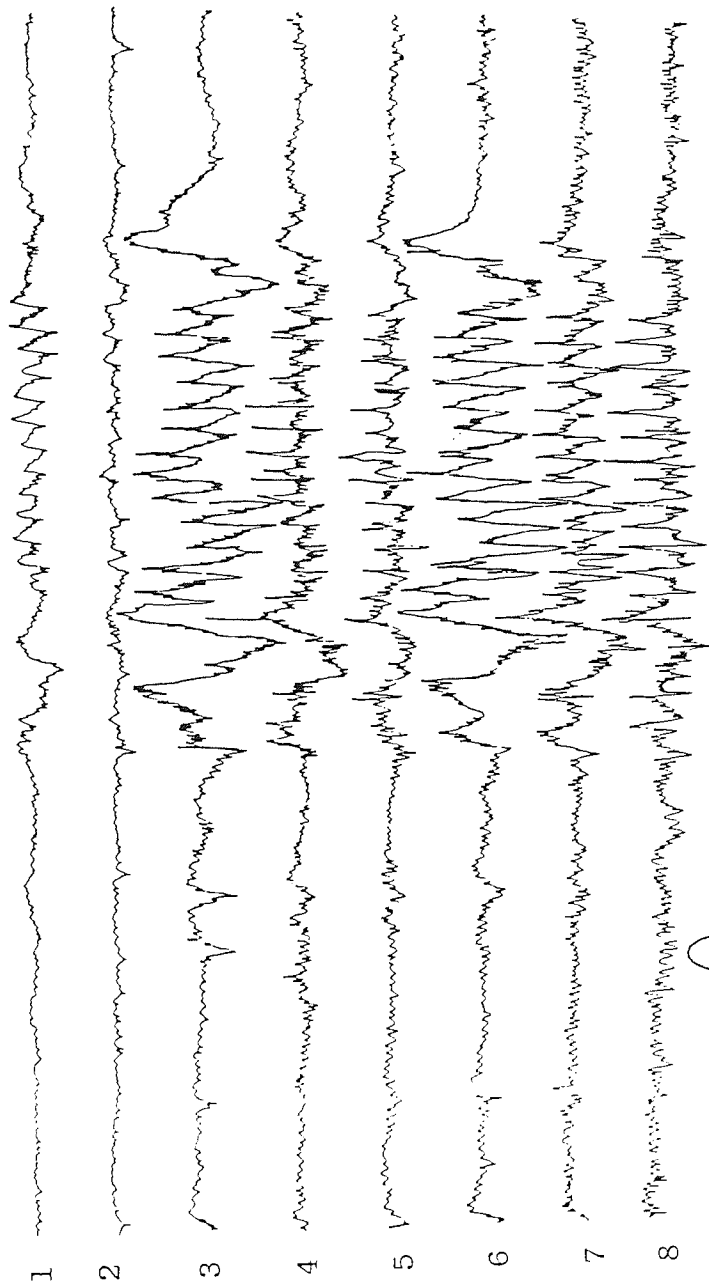
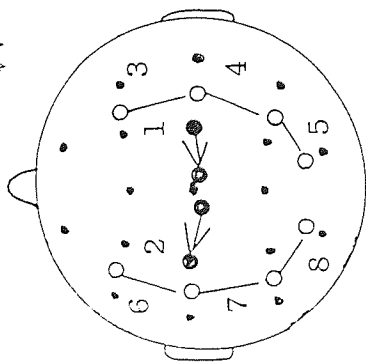


FIGURE 3.18 TOOTH BRUSHING



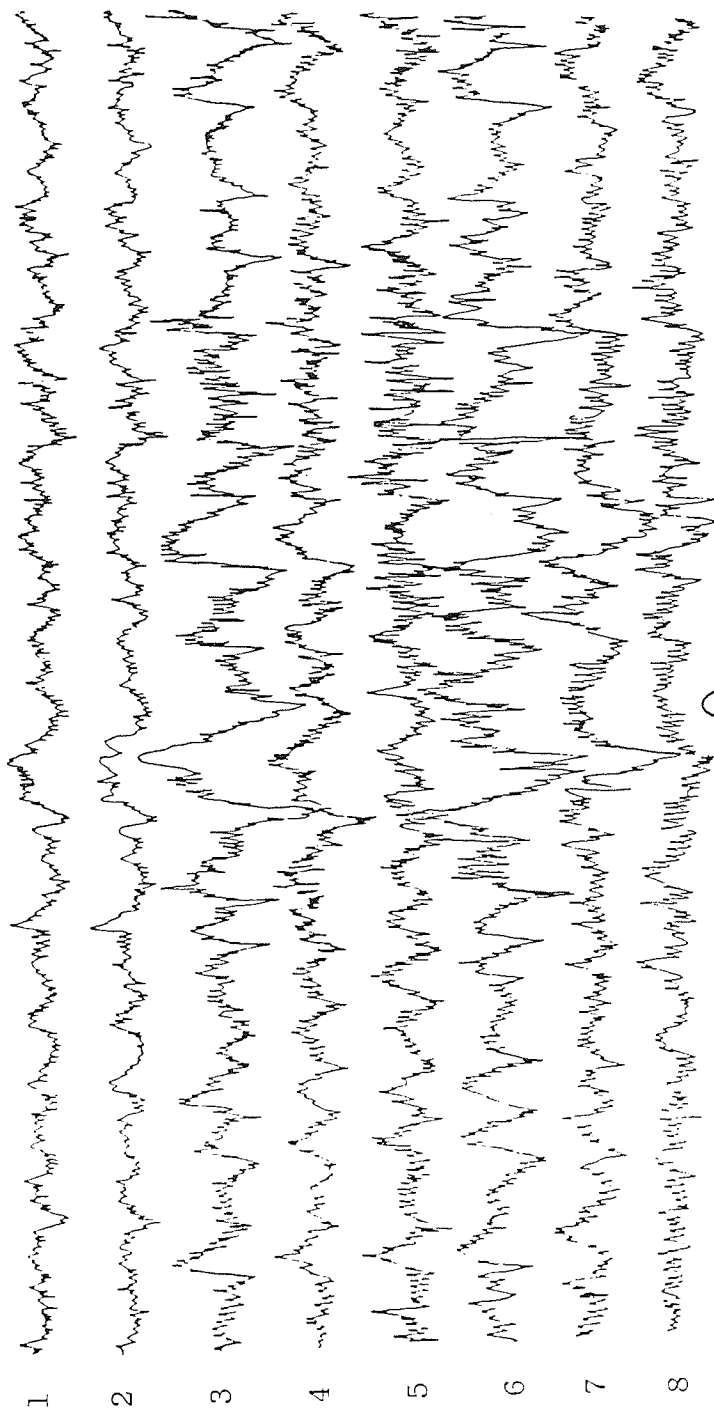
B.B AGE 40



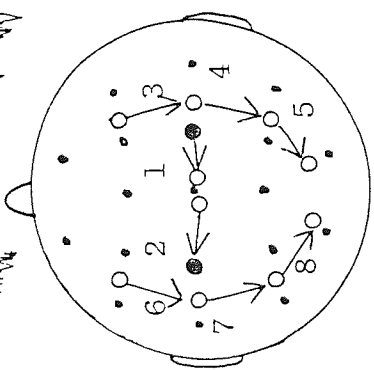
100uV
|
1sec

TOOTH BRUSHING

FIGURE 3.19



P.K AGE 21



100uV
1sec

FIGURE 3.20 BRISK WALK

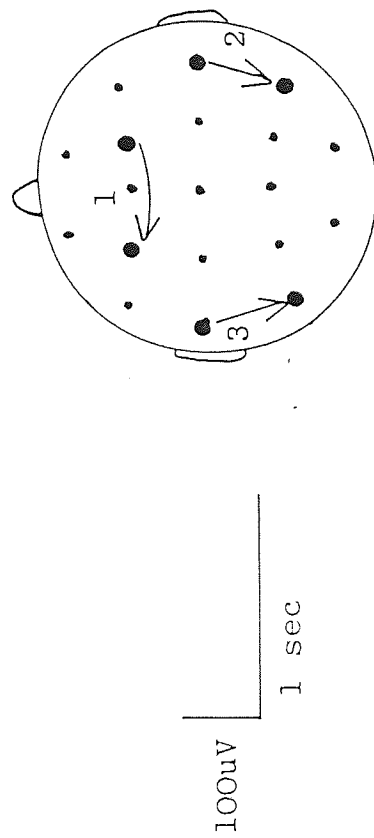
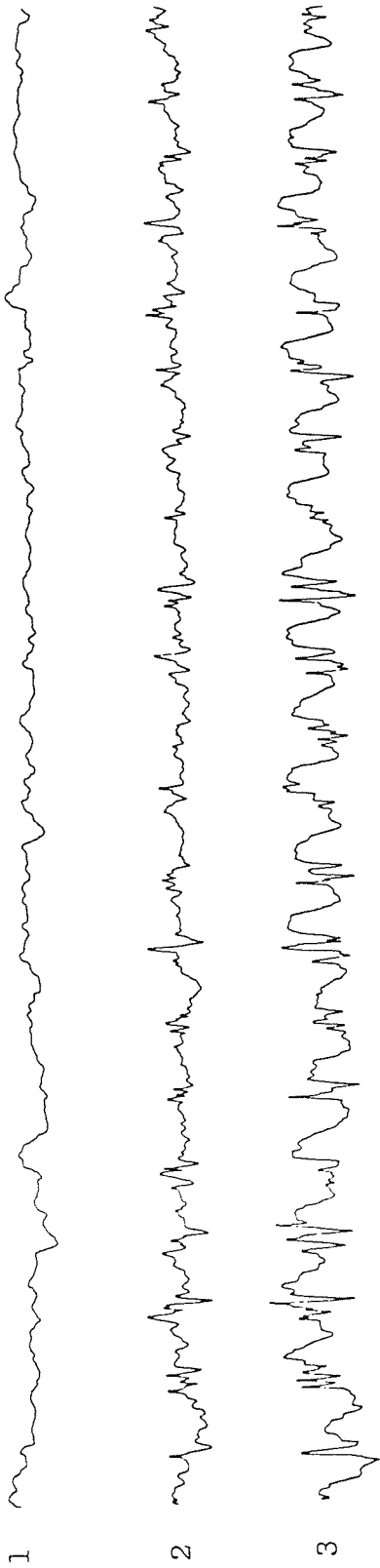


FIGURE 3.21 RUNNING

A comparison between on head and off head preamplifiers

The scalp mounted preamplifiers were a major breakthrough in ambulatory monitoring because they prevented lead movement artefact between the electrode and the preamplifier. A technique of "active screening" has since been developed which has allowed the preamplifiers to be returned into the recorder itself so that less glue is required in the hair. Today, the electrodes are simply plugged into small connectors which are worn in a collar around the patient's neck. A stress loop must be formed in the electrode lead and glued down onto the scalp to prevent undue movement prior to the connection with the screened leads.

This method saves considerable time both in recorder application and removal. In order to ensure however, that this would not be detrimental to the quality of the recording, the following experiment was performed.

Two 8 channel recorders were applied to the scalp of a volunteer subject. A recorder with the old on head preamplifiers was placed over the left hemisphere and one with the new off head preamplifiers was placed over the right hemisphere. The final channel from each recorder was placed in parallel between the Oz and Pz positions so that the traces obtained could be accurately correlated (Figure 3.22). Impedence was reduced to less than 2Kohms in each pair of electrodes.

The subject was then asked to perform a range of actions which produced the artefacts in Figures 3.23 to 3.35. He was asked to press the event buttons on both recorders at the beginning and end of each task. The resulting artefacts were printed onto a pen-writer EEG machine and the same time segment from each tape recording was extracted.

Although several of these artefacts are similar to those seen earlier, the topographical distribution is much clearer and allows for easier differentiation from genuine abnormality.

Figure 3.23 shows how massive signals can be produced at one sight by local scalp movement. The lack of spread to adjoining channels is often characteristic of artefacts arising from the electrodes themselves. No difference can be seen between the two recorders.

In Figures 3.24 to 3.27 there is slightly more muscle activity from the on head recording which probably arises from the subject himself. Chewing artefact is clearly maximal in anterior and mid temporal regions whilst nodding tends to produce more muscle activity posteriorly. Eye movements associated with nodding probably accounts for the slow activity seen anteriorly. Again no differences emerge between the two recorders.

Slow head turning (Figure 3.28) again produces a slow artefact anteriorly, probably due to eye movement rather

than head movement. Various amounts of head shaking (Figures 2.29 and 3.30) produce muscle artefact and slow waves. In the more central and anterior channels muscle activity is less obvious. In Figure 3.29 and also in later figures, artefact is accentuated in channel 7 of the "on head" recorder. This was thought to be due to a loosening of the bond between the scalp and the amplifier. A loose electrode would have caused artefacts to be common to two channels so this seemed unlikely.

Such findings illustrate how ease of interpretation can depend on a high technical standard. In Figure 3.34 pseudo-spike and wave activity is seen on channel 7 produced again, by running as seen previously.

In conclusion, no difference was found between the quality of recording obtained using on head or off head pre-amplifiers. It was therefore assumed that the new technique would save considerable time and provide recordings which were of equal quality to those obtained previously.

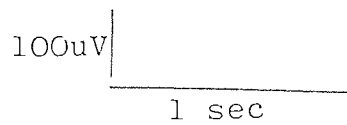
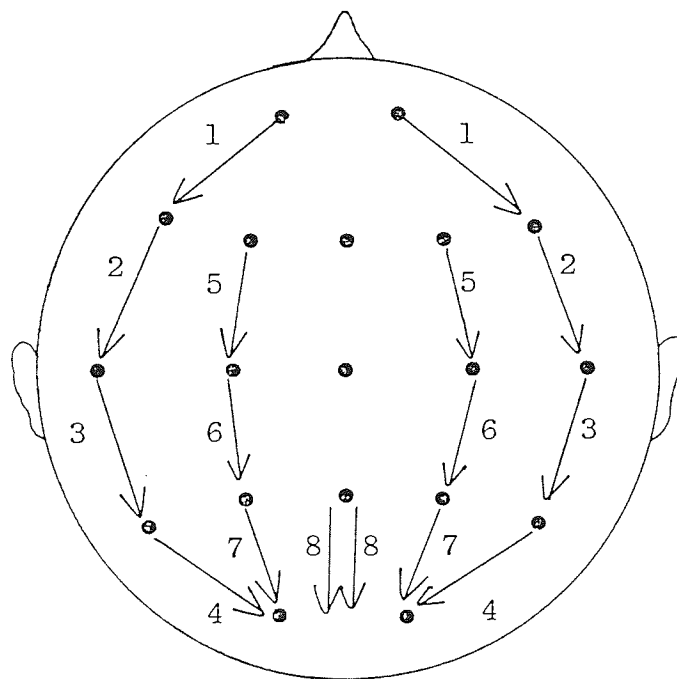


FIGURE 3.22 MONTAGE USED FOR COMPARING ON HEAD AND OFF HEAD PREAMPLIFIERS

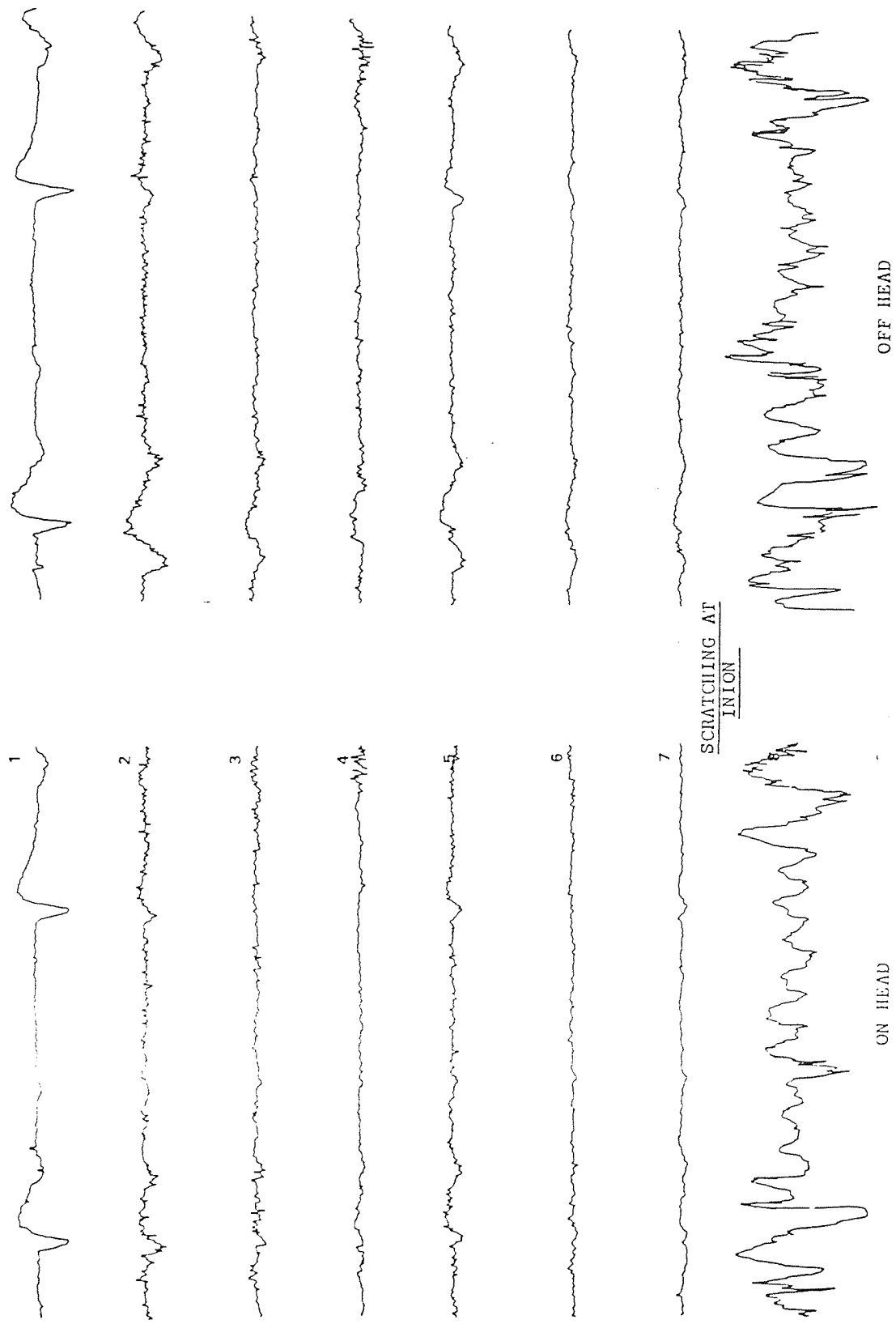


FIGURE 3.23

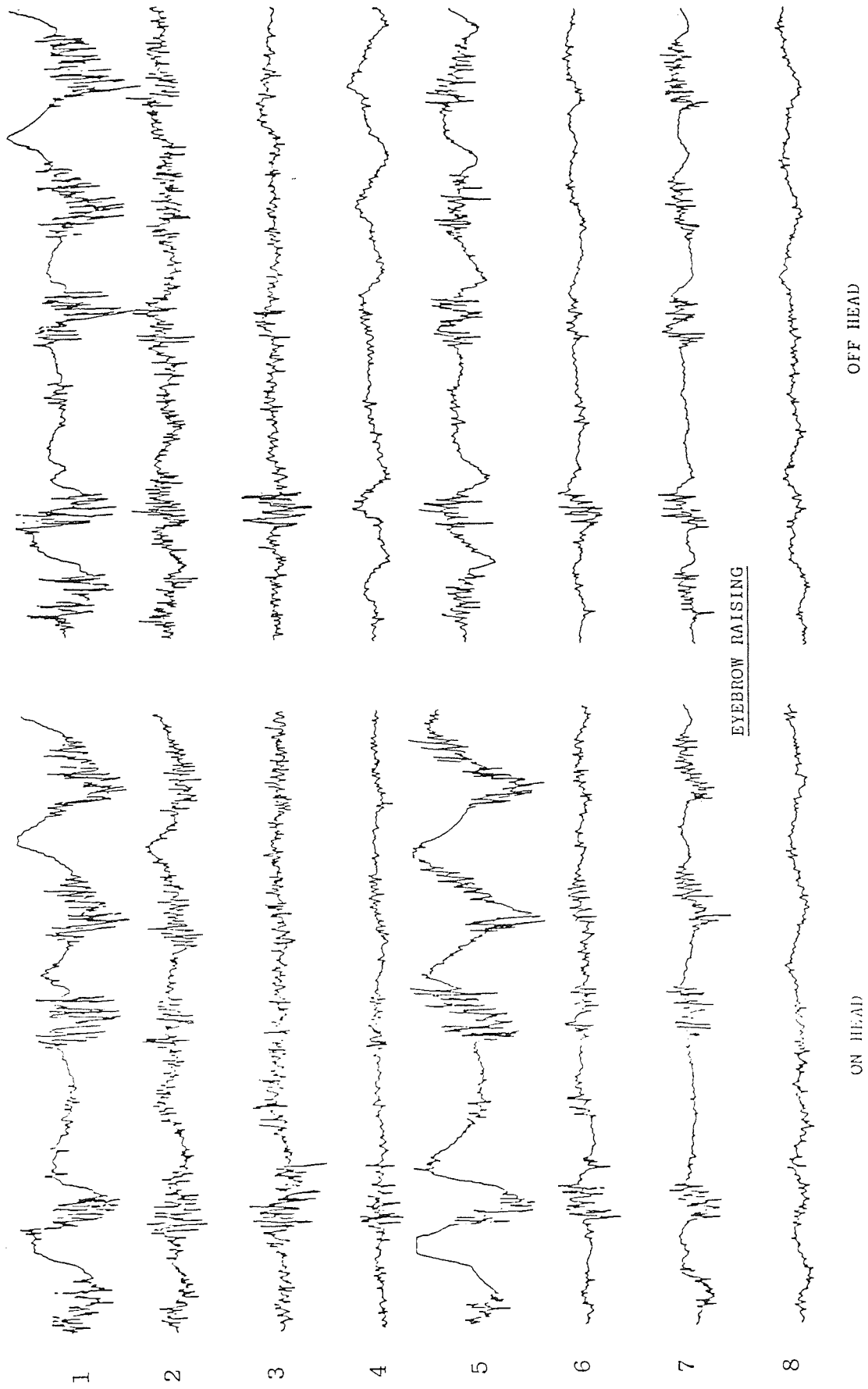


FIGURE 3.24

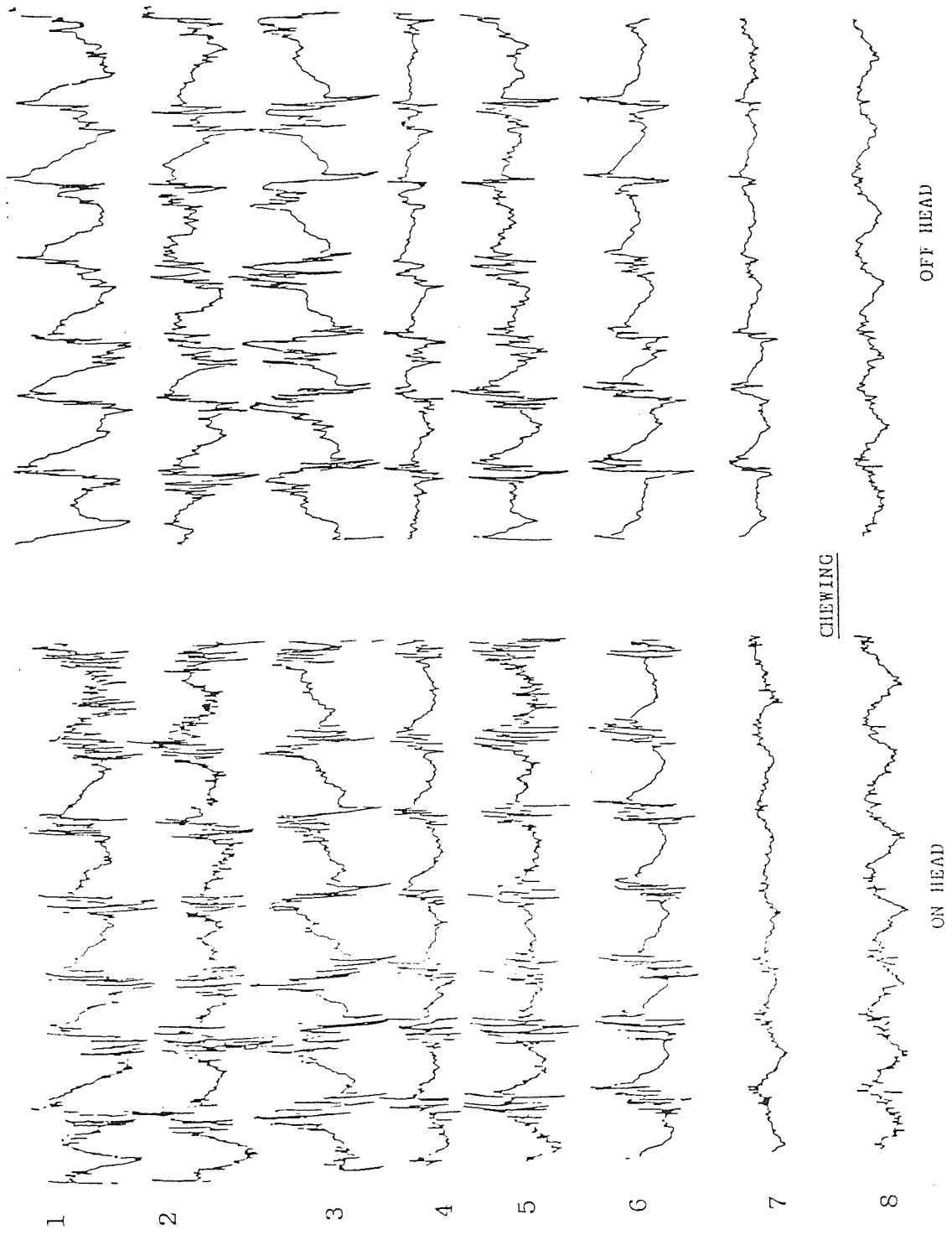


FIGURE 3.25

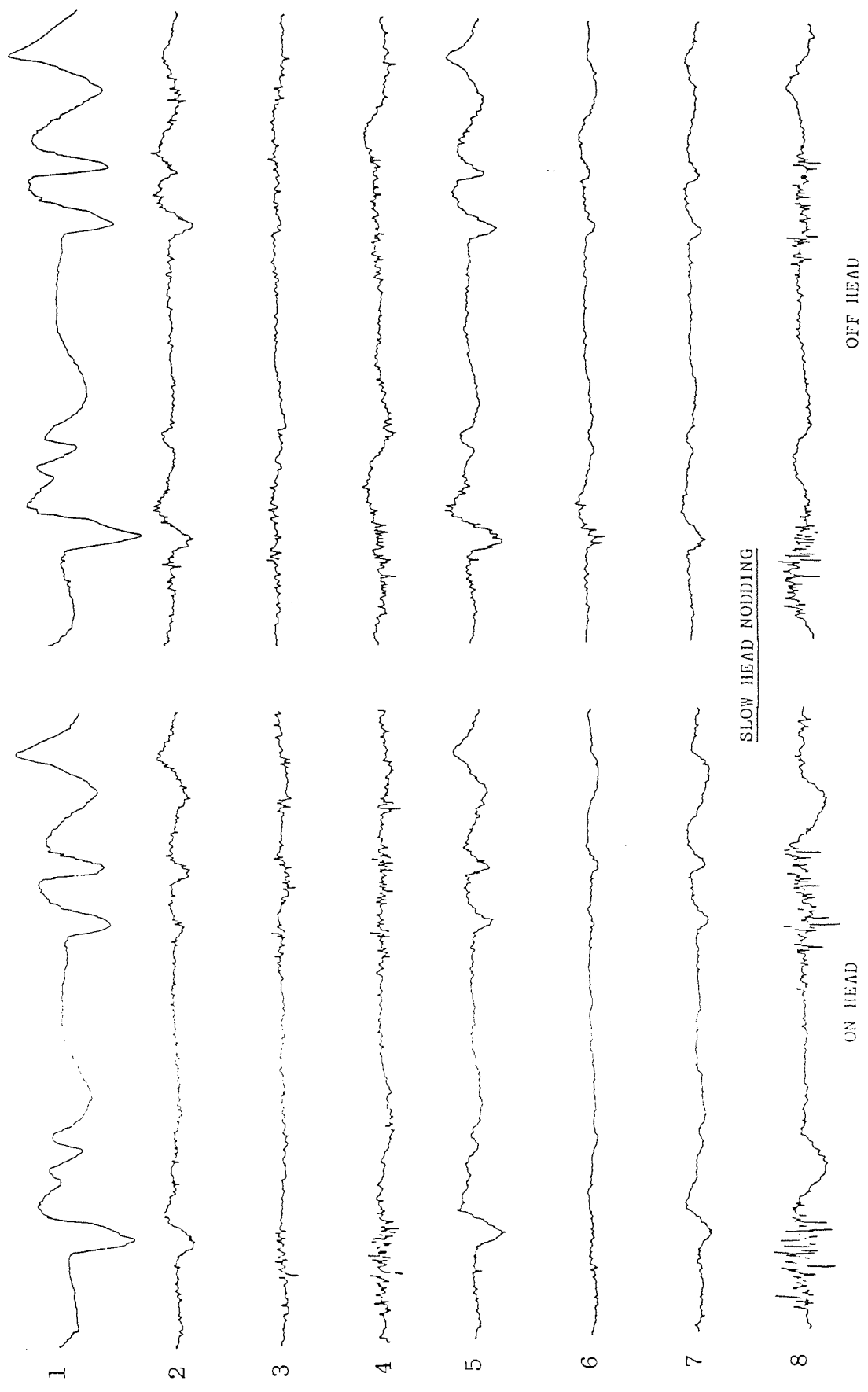


FIGURE 3.26

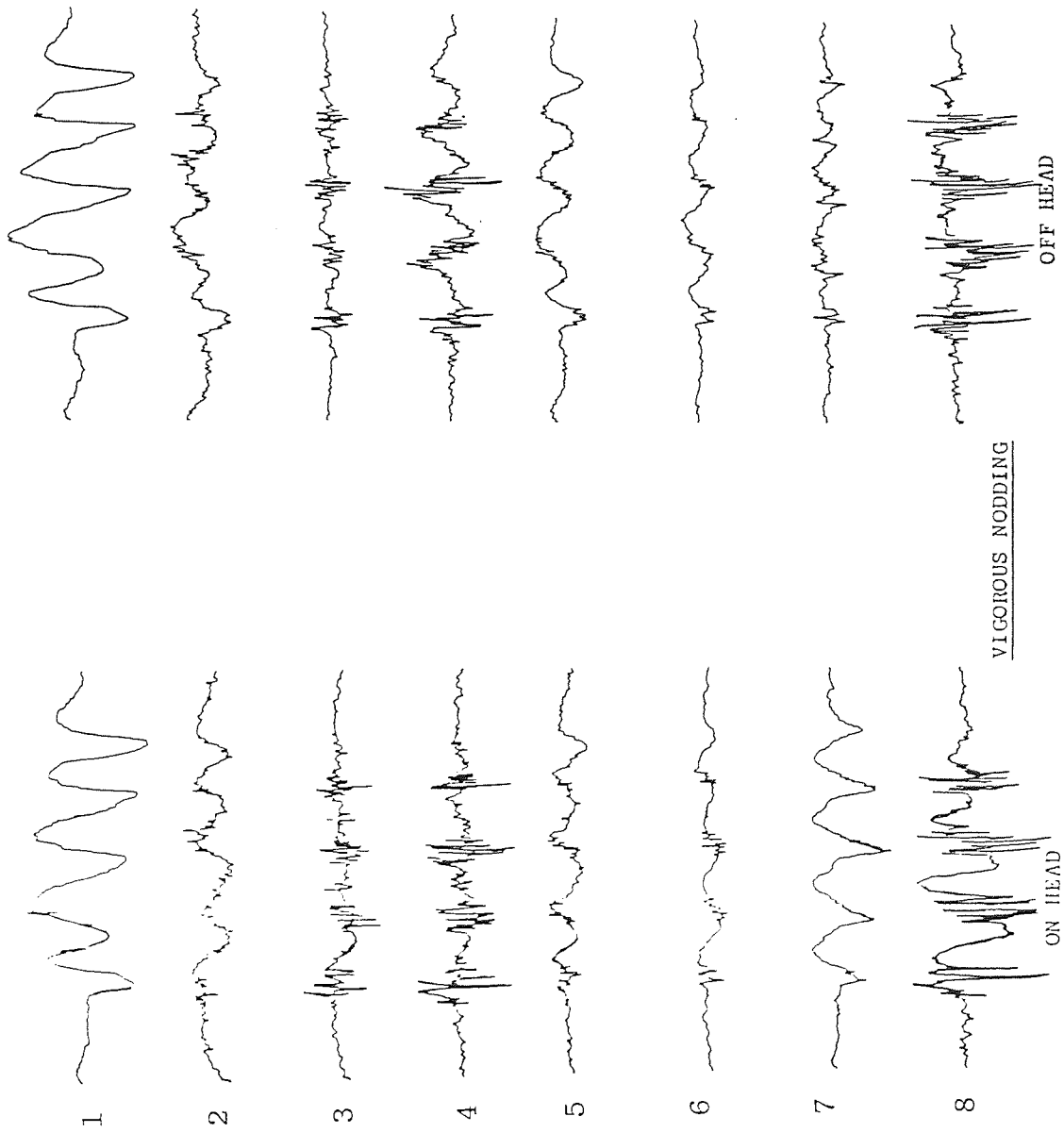


FIGURE 3.27

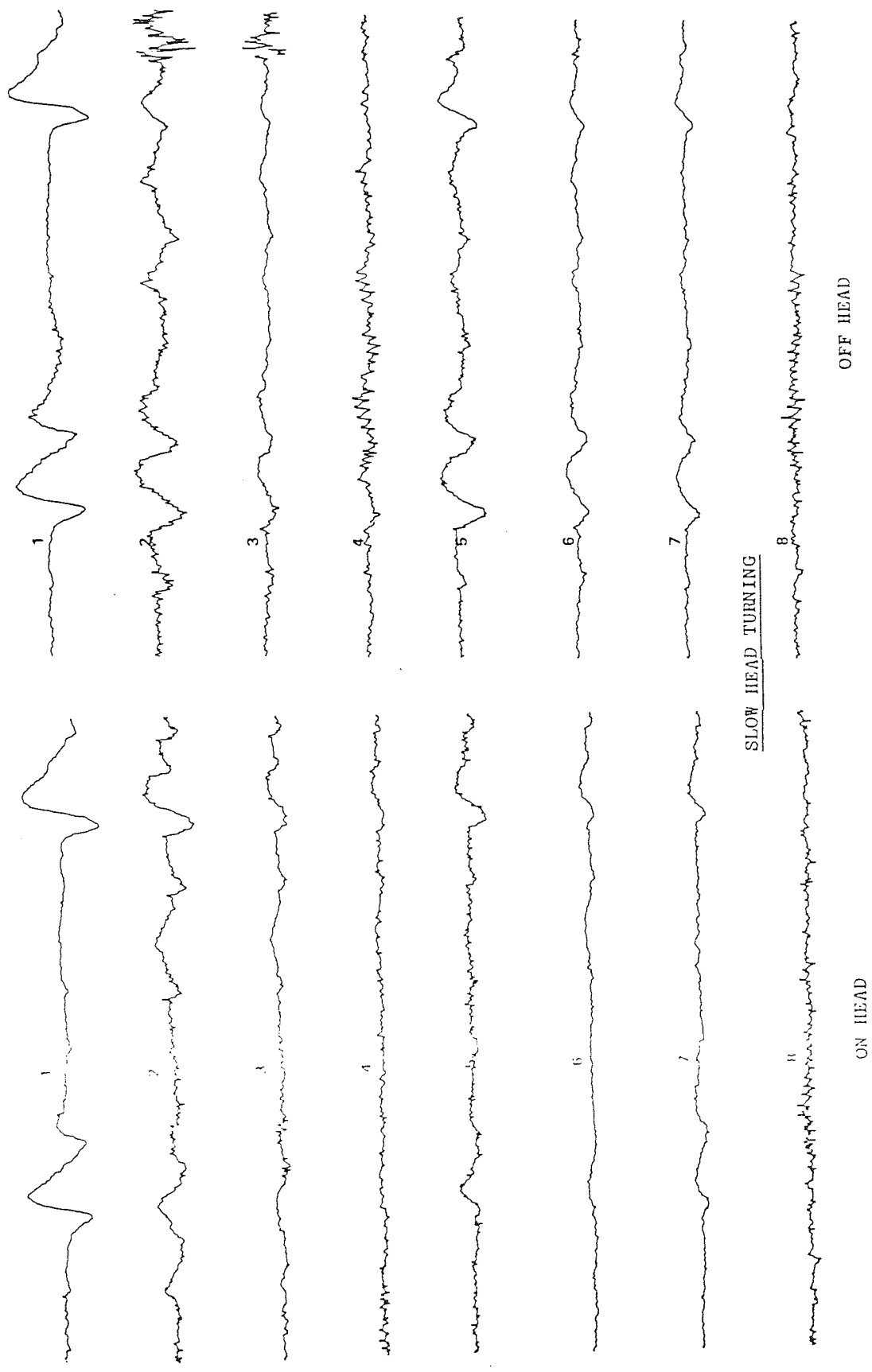


FIGURE 3.28

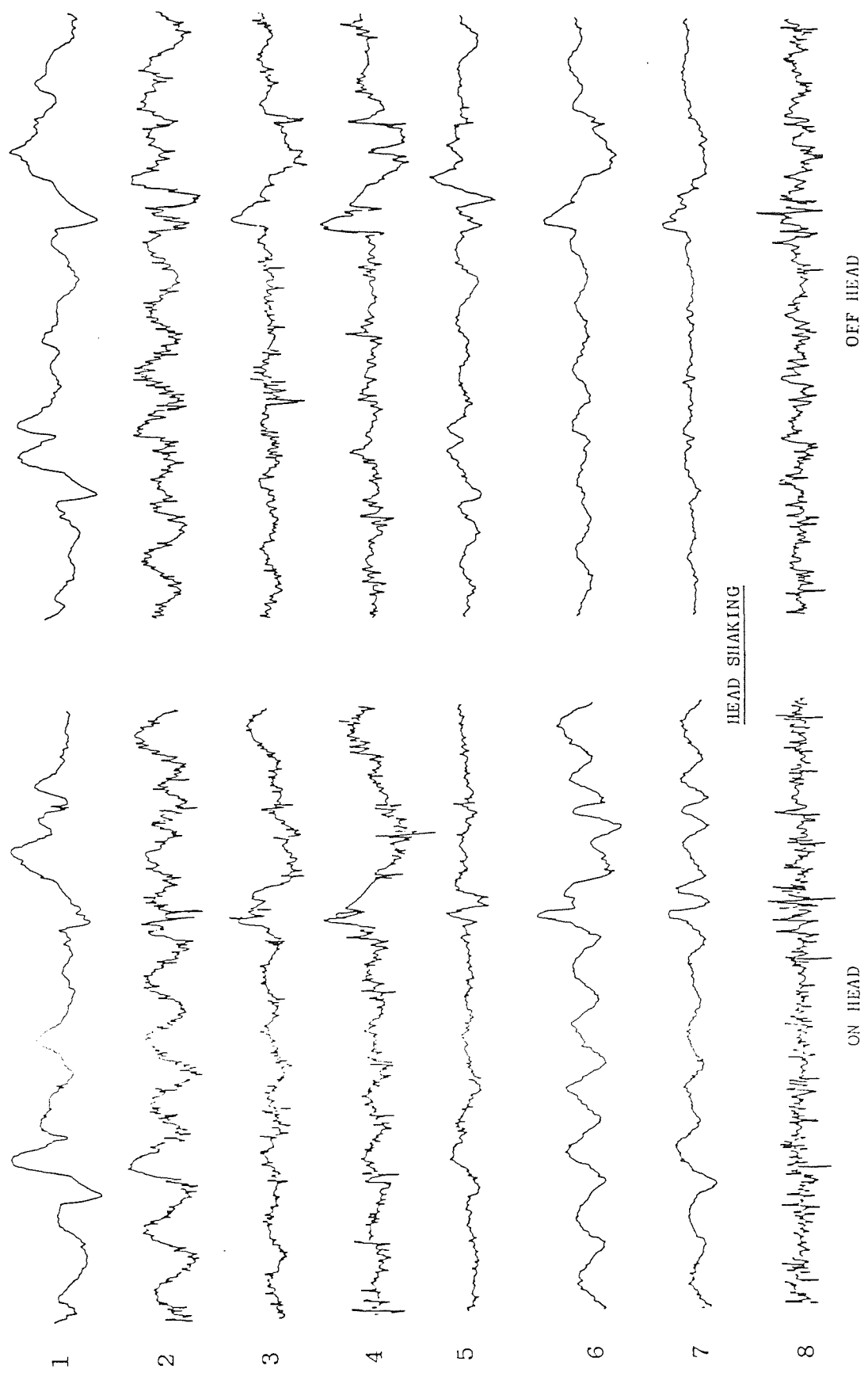


FIGURE 3.29

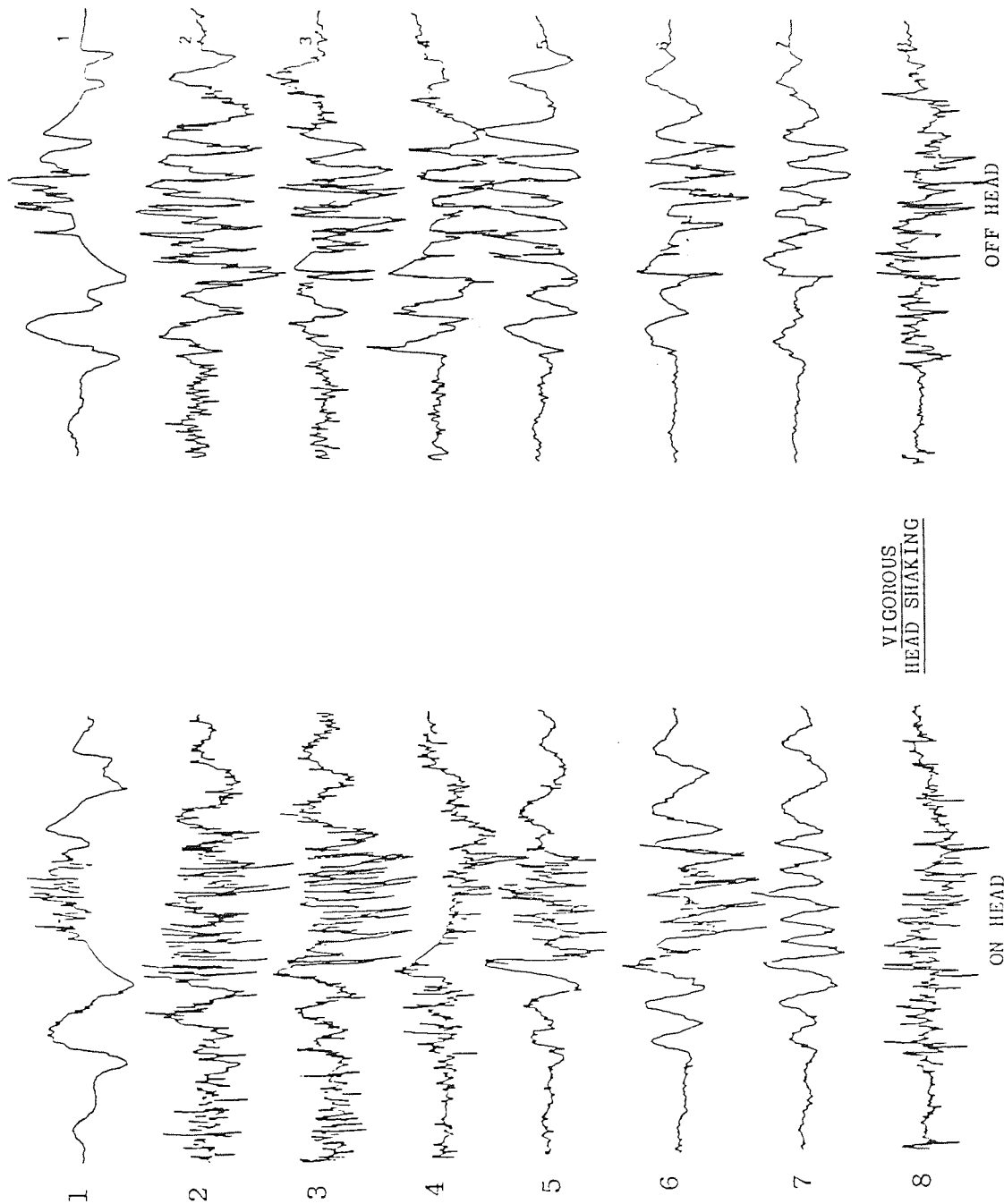


FIGURE 3.30

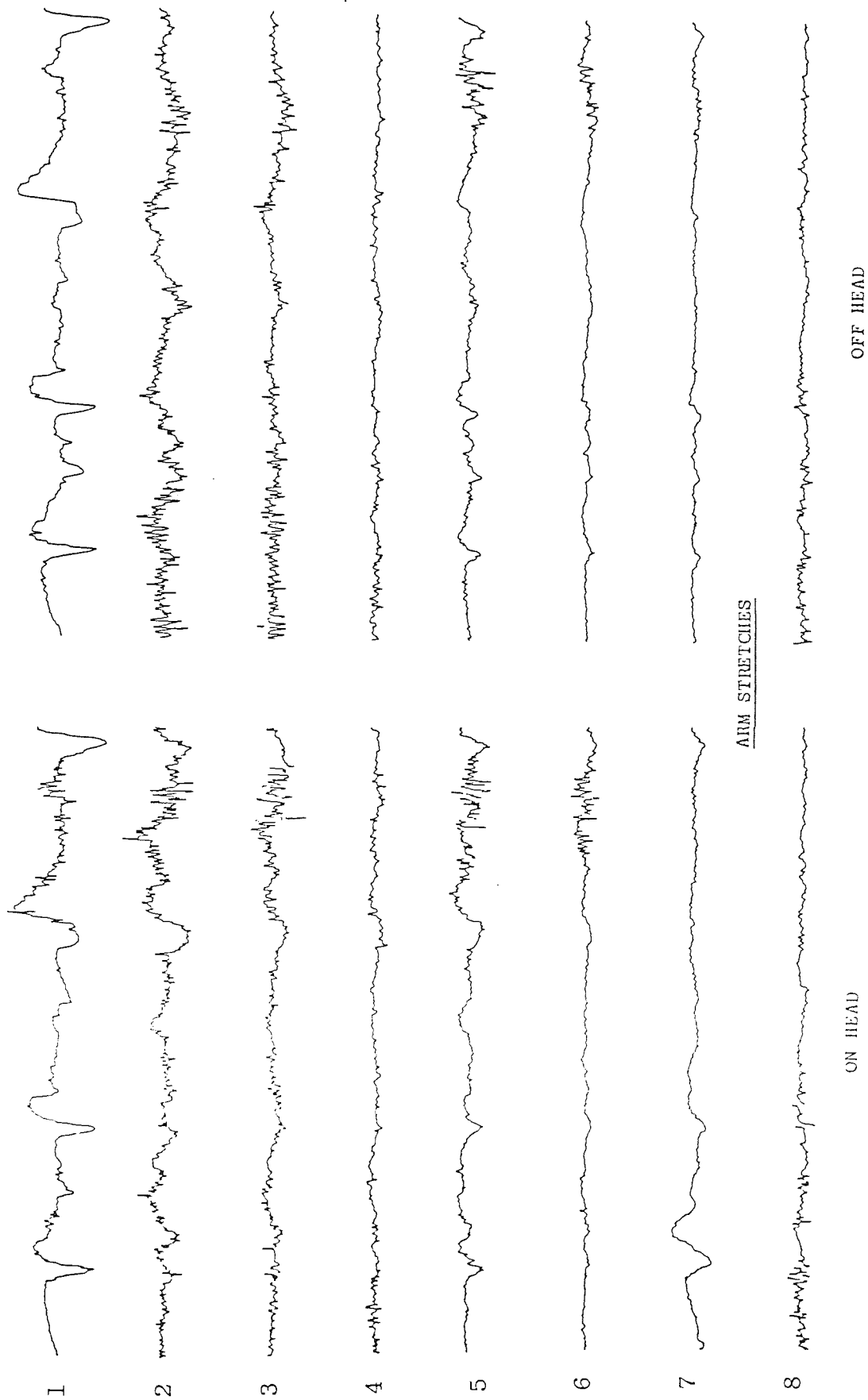
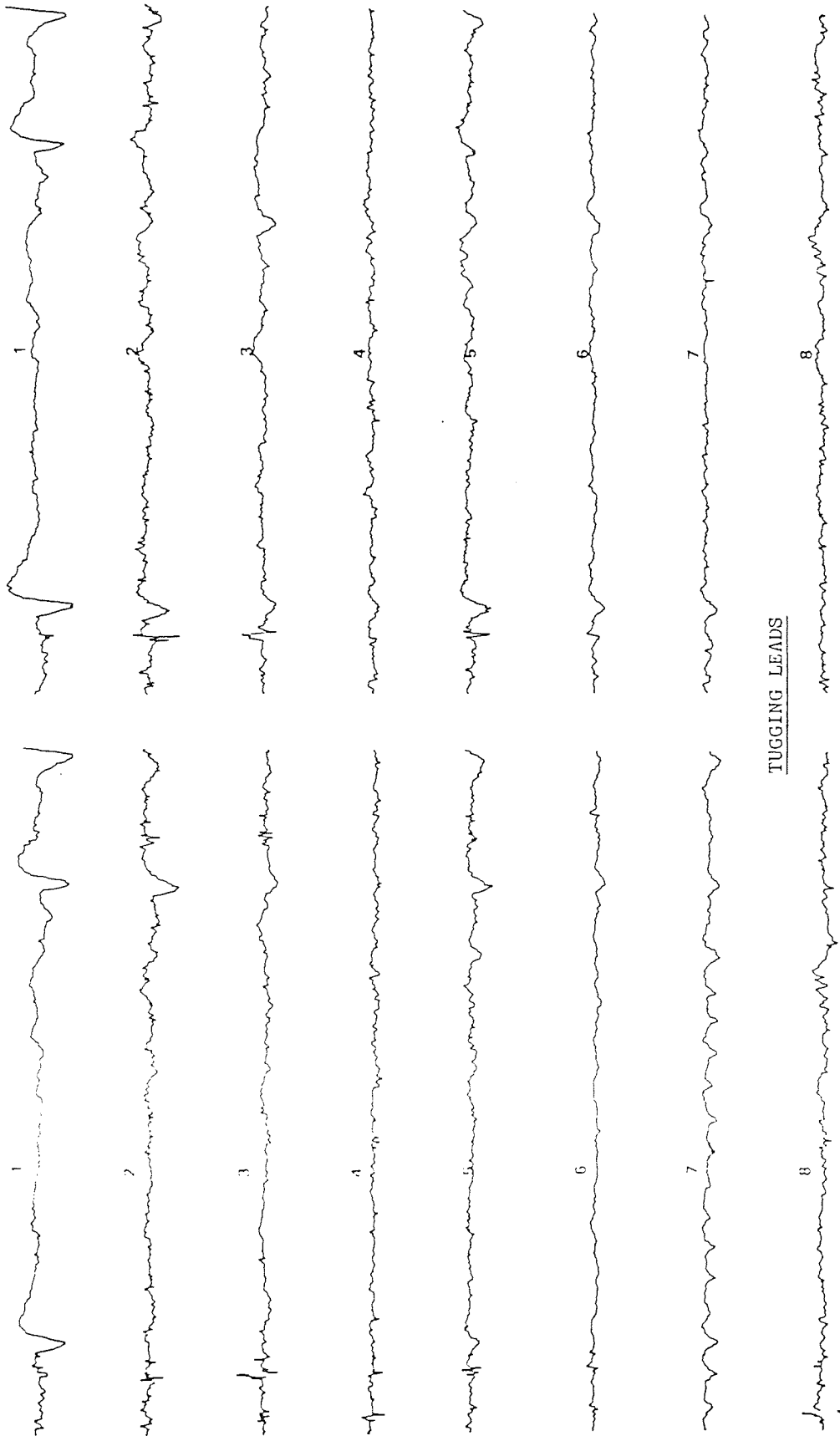


FIGURE 3.31



OFF HEAD

ON HEAD

TUGGING LEADS

FIGURE 3.32

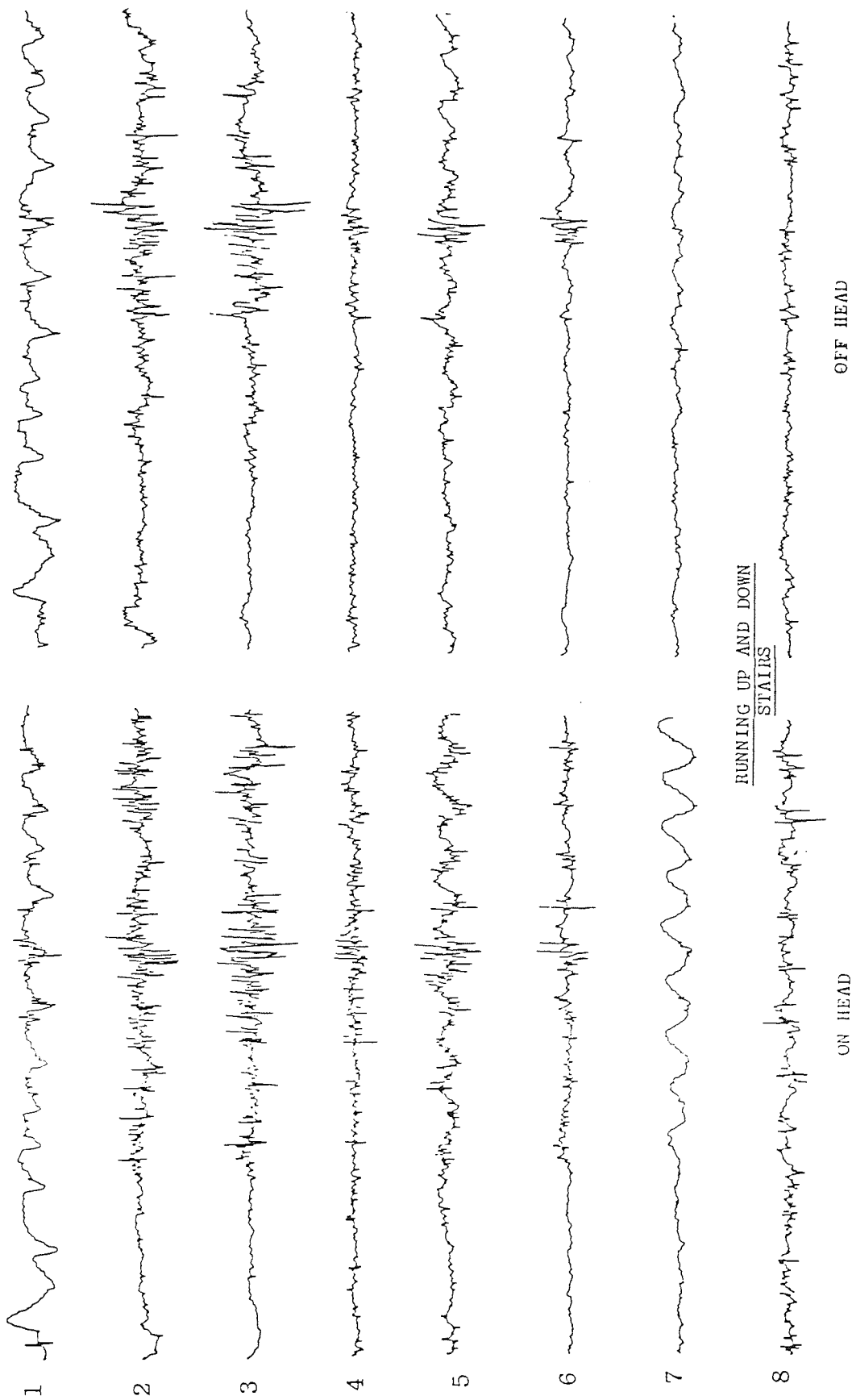


FIGURE 3.33

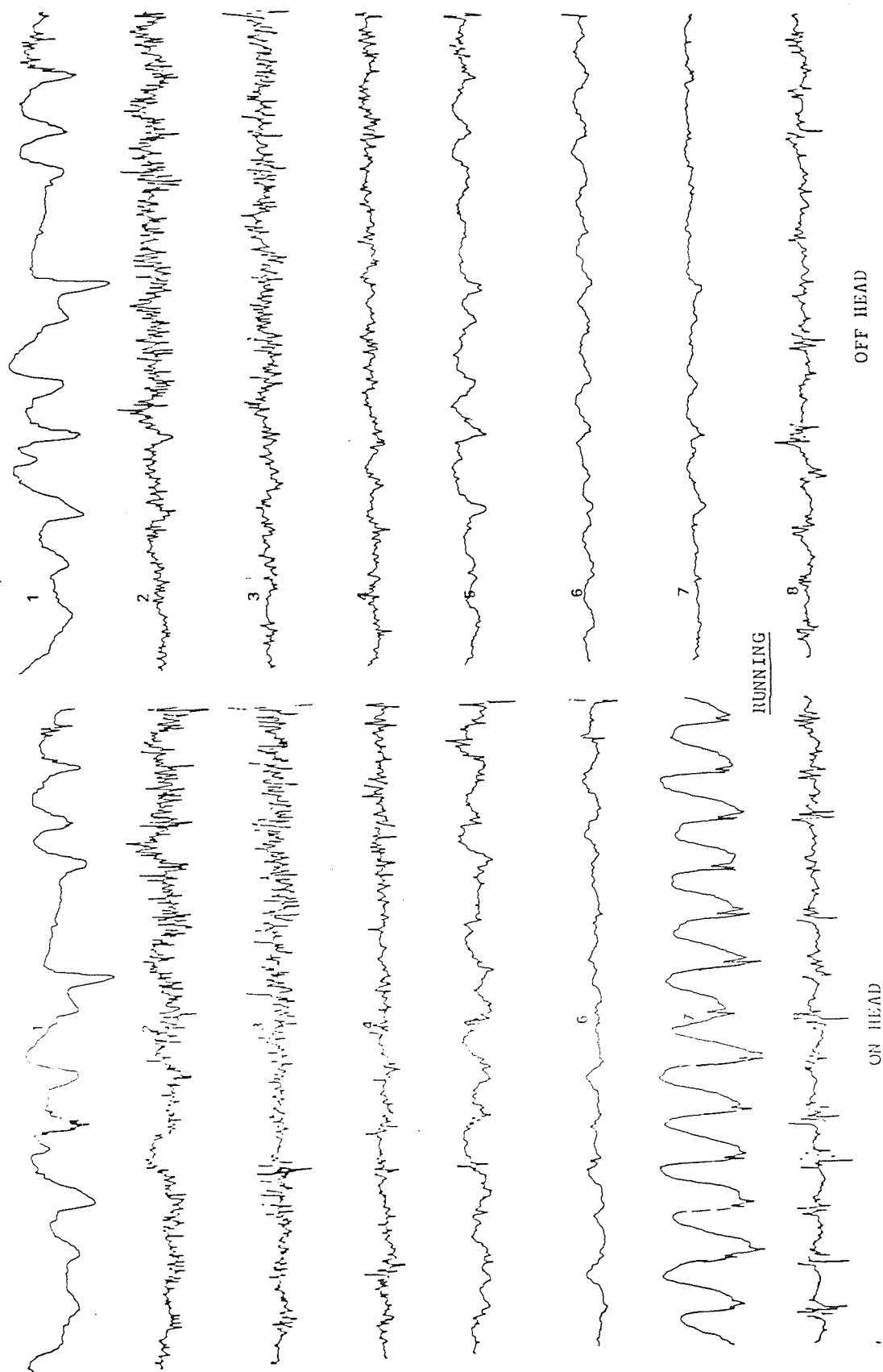


FIGURE 3.34

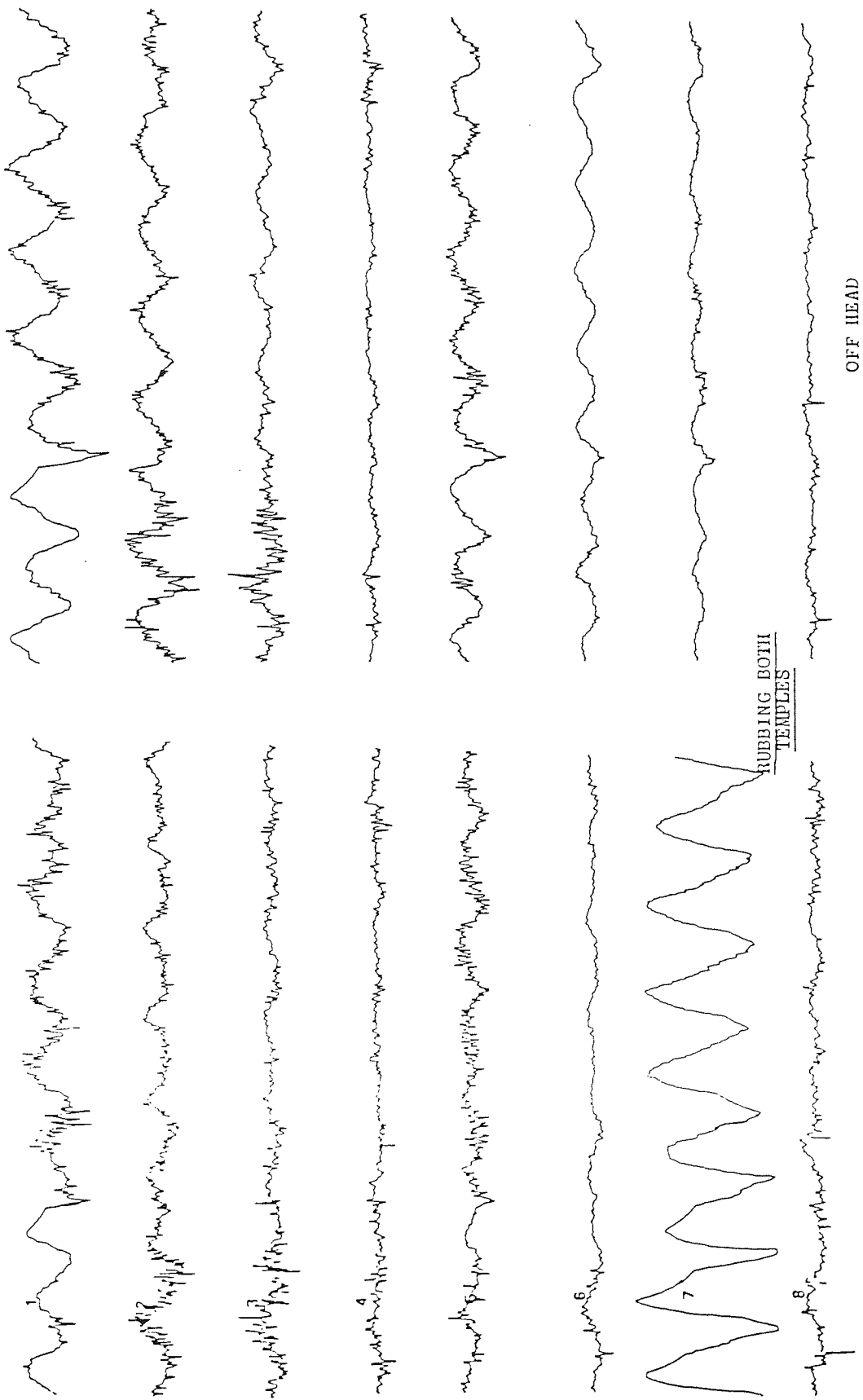


FIGURE 3.35

A comparison of tin and silver electrodes

Traditionally, EEG recordings are made with silver/silver chloride electrodes which have good recording properties (Cooper, Osselton and Shaw 1974). However, these electrodes quickly lose their silver chloride layer with frequent usage.

Ambulatory recording requires a high technical standard which entails frequent re-chloriding of electrodes which is very time consuming.

Blumhardt and Oozeer (1981) experimented with electrodes encased in a plastic cup but found them to be of little advantage. Morris and Luders (1985) report that gold plated electrodes are more convenient but are expensive. Other authors (Callaghan and McCarthy 1981) have reported that tin electrodes are routinely used for ambulatory recording without being detrimental to the quality of recording obtained.

Eight tin electrodes were therefore acquired and compared to conventional newly-chlorided silver electrodes.

METHOD

Subjects:

Ten subjects took part in the experiment, nine females and one male aged between 16 and 44 years.

Apparatus:

Two silver/silver chloride electrodes and two tin electrodes were applied to the scalp of each subject using Collodion glue and Neptic gel as an electrolytic interface. Impedance was tested using an Oxford Medilog Systems XI-1 electrode impedance tester.

Procedure:

The study was single blind. Each pair of electrodes was randomly allocated to either the right or left side of the subject's head and concealed in the hair. Electrodes were applied at 10.00hrs. Initially, impedances were reduced to 2Kohms or less. Subjects were then asked to measure the impedance between each pair of electrodes at two hourly intervals with an eight hour interval during sleep. Electrodes were removed at 10.00hrs the following day.

RESULTS

Analysis:

Since the scale of the impedance meter was non-linear and after 50Kohms terminated at infinity, it was necessary to analyse results non-parametrically. The sign test was therefore used (Siegel 1956). This test is appropriate for determining whether any difference exists between two related samples when quantitative measurement is impossible.

Results indicated that there was no significant difference between the impedance of tin and silver electrodes over the 24 hours ($p = 0.58$).

CONCLUSIONS

Tin electrodes would appear to be as effective as silver electrodes in maintaining adequate impedance levels for prolonged recording. In situ testing was however necessary before adequate conclusions could be drawn. For this purpose the following preliminary investigation was carried out.

STUDY 2

Ten clinical ambulatory EEG investigations were carried out using either 3, 4 or 8 channel Oxford Medilog

recorders. At least one pair of tin electrodes was incorporated into each recording. During playback any 50cps interference was noted in both tin and silver electrode channels and also any other malfunction. Results are given below:

Six investigations: No faults on tin or silver channels.
Total number of tin channels, 10.
Total number of silver, 19. Total recording time 284 hours.

Four investigations:

1) 2 tin channels (linked)

6 silver channels

After 14 hours 50cps appeared on one tin channel and the adjoining channel appeared reduced in amplitude

2) 1 tin channel

2 silver channels

After 14 hours one silver channel appeared reduced in amplitude

3) 1 tin channel

2 silver channels

After 15 hours, 50cps was present on all channels (possibly some element of patient interference)

4) 2 tin channels (linked)

6 silver channels

After 23 hours there was 50cps on 3 silver channels

(In no case was interference such that interpretation of results was rendered impossible. In fact, in many cases 50cps was recognised only by sound on playback).

DISCUSSION

It would appear that as yet there are no faults specifically confined to the use of tin electrodes. However, it should be emphasised that this was only a preliminary study, more extensive investigations being required.

Method of Analysis

Details of investigations performed and results obtained were processed on an RML 380Z microcomputer. A programme entitled 'Filespec' was designed to set up headings under which data could later be entered. The following headings were used each having sub-categories into which details were later entered by number using a programme called 'Ddataspec'.

Patient's initials

Patient's age (to nearest year)

Patient's sex: 1 Male
 2 Female

Duration of recording (days)

Basic EEG: 1 Normal
 2 Abnormal
 3 Other (attack on EEG, or photo-
 sensitivity)

(Specific EEG abnormalities were collated by hand as this involved the use of too many sub-categories).

Reason for referral:

1 Tonic clonic seizures (a clinical description of loss of consciousness, jerking and no warning)

- 2 Absence seizures
- 3 Partial seizures (including simple and complex, as these could not be distinguished on the basis of descriptions available, and benign rolandic)
- 4 Myoclonic seizures
- 5 Undiagnosed episodes (including syncope, vaso-vagal, cardiac and any loss of consciousness without jerking. Also bizarre attacks atypical of partial seizures)
- 6 Monitoring attack frequency
- 7 Narcolepsy
- 8 Attacks in sleep
- 9 Genuine and non-genuine attacks (pseudo-seizures)

Outcome of investigation

- 1 Attack showing abnormality worse left
- 2 Attack showing abnormality worse right
- 3 Attack showing generalised abnormality
- 4 Attack showing no abnormality
- 5 No attack
- 6 Attack unclear or artefact
- 7 Technical failure
- 8 Spike and wave controlled
- 9 Spike and wave not controlled
- 10 Genuine and non-genuine attacks
- 11 Genuine attacks only
- 12 Non-genuine attacks only
- 13 Sleep abnormality
- 14 Background abnormality

Type of recording: 1 3 EEG
2 4 EEG
3 3 EEG, 1 ECG

Referring Consultant 1 Psychiatrist
2 Paediatrician
3 Neurologist
4 Neurophysiologist
5 Physician
6 Epileptologist

Where recording 1 Home
took place 2 Hospital
3 Home and Hospital

Three and eight channel investigations were listed separately. The reason for referral was modified slightly for 8 channel investigations to include attack localisation. The heading entitled 'type of recording' was also excluded as all recordings consisted of eight EEG channels.

Finally a programme entitled 'Ambsort' was used to link across categories so that different headings could be matched. The number of patients resulting from each matched pair were entered into two large matrices, one for 3 channel and one for 8 channel investigations. In order to check the entire listing, a programme entitled 'Listspec' could be used to produce a complete table.

The Effect of Recording Environment

Patients were encouraged whilst being recorded to continue their normal daily activities as far as possible. Those who felt too embarrassed, or felt there would be insufficient understanding from work or school colleagues remained at home. Some children actually spent the day doing homework. Unless it was thought that the work environment had a direct influence on attacks no one was pressurised to go to work or school. Many patients were either unemployed or on sick leave due to the nature and frequency of their attacks. Seventy eight per cent of investigations were therefore made with the patient remaining at home or going to work or school (Table 3.6).

A relatively smaller number of patients (21%) were in hospital at the time of the investigation. Most of these patients were in psychiatric hospitals or on psychiatric wards in general hospitals for observation of attacks or possible adjustment of anticonvulsant medication. Unfortunately, these recordings often created problems when nursing staff changed shift and failed to pass on their instructions with regard to the investigation.

The number of technically inadequate recordings and the number of attacks which could not be distinguished from artefact were therefore compared for hospital and home environments.

TABLE 3.6

Effect of where recording was made
on outcome of investigation

	Home	Hospital	Both*
No Attack	94 (48.21%)	30 (57.69%)	2 (66.67%)
Attack Recorded	92 (47.18%)	17 (32.69%)	1 (33.33%)
Attack Equivocal	5 (2.56%)	2 (3.85%)	0
Technical Failure	4 (2.05%)	3 (5.77%)	0
Total 3 and 8 Channel Recordings	195 (78%)	52 (21%)	3 (1%)

* some patients went home for weekend leave mid-way through recording

Results showed that problems were encountered in a total of 5% of recordings made at home and 10% of recordings made in hospital.

Several patients reported that the hospital environment seemed to have an inhibiting effect on attacks. The number of investigations carried out in hospital in which attacks did not occur was therefore compared to the number made at home. Results showed that 58% of investigations carried out in hospital did not include attacks compared to 48% of those carried out at home.

A chi-square test showed no significant differences between these two groups ($\chi^2 = 3.1$, d.f. = 3).

It would therefore appear that hospital admission did not have an adverse effect on the quality of recording obtained or reduce the likelihood of attacks occurring.

Comparison of 3 and 8 channel recordings

In order to assess differences between 3 and 8 channel recording the outcome of investigations was examined. Table 3.7 shows that slightly more 3 channel investigations were technically inadequate.

Overall, attacks were recorded in 53.5% of investigations. Seven per cent of investigations showed abnormalities which were not present in the basic EEG although no attack actually occurred. Most of these abnormalities were

TABLE 3.7

Comparison of the outcome of 3 and 8 channel

investigations

Outcome	3 channel	8 channel	Total
Attack Recorded	86 (52.12%)	29 (58%)	115 (53.49%)
No Attack	62 (37.5%)	16 (32%)	78 (36.28%)
No attack but abnormality not clear in basic	11 (6.67%)	4 (8%)	15 (6.98%)
Technical Failure	6 (3.64%)	1 (2%)	7 (3.26%)
Total	165	50	215*

* does not include patients referred for monitoring frequency of sub-clinical spike and wave discharges

TABLE 3.8

Comparison of EEG changes during attacks
recorded on 3 and 8 channel recorders

EEG during attack	3 channel	8 channel	Total
EEG abnormal	28 (32.56%)	12 (41.38%)	40 (34.78%)
EEG no abnormality	51 (59.30%)	17 (58.62%)	68 (59.13%)
EEG doubtful	7 (8.14%)	0	7 (6.09%)
Total	86	29	115

present during sleep and will be discussed later.

The efficiency of 3 and 8 channel recording to detect abnormality during attacks was also examined (Table 3.8). Results showed that a similar percentage of 3 and 8 channel attacks showed no EEG abnormality. However, fewer attacks showed abnormality when recorded on the 3 channel machine and this appeared to be dependent on the number of investigations in which there was difficulty in deciding whether abnormality was genuine or artefact. None of the 8 channel investigations actually included attacks in which the EEG abnormality was doubtful.

Overall, 35% of investigations included attacks which showed EEG abnormality and 59% showed no abnormality. Although some recordings included more than one attack the EEG change was always consistent, even in patients referred with possible genuine and non-genuine seizures.

Classification of recorded attacks by the EEG and clinical description

It was often found that details given in referral letters were insufficient to allow complete classification of the attacks. Therefore although patients were tentatively classified by referral, as described in the method of analysis, ultimately only 3 or 4 broad categories were used as shown in Table 3.4 and 3.5.

The final post-hoc classification was based upon the

clinical description of attacks when available, and the EEG changes during the recording. Results can be seen in Table 3.9.

Attacks which showed focal EEG changes were the type of seizure most commonly recorded, 34 (85%) of these confirming the classification by the clinical description. Differentiating by clinical description between right and left sided partial seizures was difficult and it was only possible to classify 3 in this way. They could however, be classified on an EEG basis and it would appear that right sided abnormalities were the most common. Several of these abnormalities may have become secondarily generalised either from a clinical or an EEG point of view but the distinction was often unclear particularly when only 3 EEG channels had been used. It was also impossible to distinguish on clinical grounds between simple and complex partial seizures as insufficient information was available.

Attacks showing generalised spike and wave activity were the next most commonly found. Seventy per cent of these could also be classified by the clinical description and were often distinct from partial seizures by a lack of post-ictal confusion.

Several attacks were extremely difficult to classify as the EEG changes and the symptomatology were very complicated.

TABLE 3.9

Types of EEG abnormality recorded
during seizures

<u>Seizure</u>	<u>Clinical Description</u>	<u>EEG</u>
Absence	7	10
Myoclonic	2	2
Tonic-clonic	3	3
Partial	15	18
(Right Partial	2	14)
()
(Left Partial	1	4)
Unclassified	7	7
Total	<u>34*</u>	<u>40</u>

* In 6 patients the clinical description was unavailable mainly because the patient was alone at the time of the attack

One patient showed both partial and generalised attacks independently, three patients showed spike and wave activity lateralised to one hemisphere and in 3 patients the description of the attack was inadequate and attacks were recorded on a 3 or 4 channel recorder making classification difficult.

Finally, primary generalised tonic-clonic seizures and myoclonic attacks were the least commonly recorded on the ambulatory EEG. The reason for this is uncertain, but may possibly reflect a lower incidence of attacks so that patients fell into the 'no attack' group. Alternatively, it is possible that tonic-clonic seizures are so easily identifiable that ambulatory recording is not required.

Value of the ambulatory EEG compared to the basic EEG

Table 3.10 shows EEG findings during attacks compared to the basic EEG. The figures in brackets indicate the number of patients in whom the EEG findings in the basic recording were similar to those recorded during attacks. Findings were considered to be similar if the EEG abnormality during attacks was lateralised to the same hemisphere as the basic EEG abnormality or if both investigations contained spike and wave activity.

Forty-five patients had normal basic EEGs and no abnormality during attacks. Twenty-seven had abnormal basic EEGs and also showed abnormality during attacks. Only

TABLE 3.10

Comparison of basic EEG and EEG during attacks recorded in
the ambulatory EEG (3 and 8 channel patients)

	Normal basic	Abnormal basic	Basic other	Total
Attacks showing no abnormality	45	18	* 4 (1)	67 (46)
Attacks showing abnormality	10	27 (9)	+ 3 (1)	40 (10)
Attacks equivocal	2	1	0	3
Total	57	46 (9)	7 (2)	110 (11)

* 2 patients photosensitive

1 patient high amplitude widespread fast activity

1 patient attack during basic showing no abnormality

+ 2 patients photosensitive

1 patient tonic-clonic seizure during basic

() Figures in brackets indicate the number of patients in whom the EEG findings in the basic recording were similar to those recorded during an attack

in 9 of these patients however, did the basic EEG show a similar abnormality to that seen during attacks.

Relatively few patients with normal EEGs (18%) showed abnormality during attacks, but more, (37%) with abnormal basic EEGs showed no abnormality during attacks.

It is interesting that only 2 patients (1.8%) actually experienced clinical attacks during the basic EEG. In total the basic EEG was consistent with the recorded epileptic attack in 10 (25%) of patients.

Table 3.11 shows the type of basic EEG abnormality found in patients who experienced attacks without abnormality. The commonest finding was a basic EEG which was too slow for the age of the patient. Bilateral slow activity, usually occurring in bursts, was also fairly common. Surprisingly, 2 patients showed spike and wave activity in the basic but not during attacks. One of these patients was photosensitive and the other was referred to clarify whether aggressive or naughty behaviour was associated with spike and wave activity which was already known to be present in conjunction with clinical absence seizures.

Table 3.12 shows abnormalities found during attacks when the basic EEG was normal. Spike and wave activity and right sided abnormalities were equally most likely to occur. As spike and wave activity is often provoked by

Abnormalities found in the basic EEG of patients
who experienced attacks showing no abnormality

<u>Basic EEG abnormality</u>	<u>Number of patients</u>
Unilateral slow or sharp	3 (2 right, 1 left)
Bilateral slow	5
Bilateral sharp	1
Spike and wave	2
Too slow for age	7
<hr/>	
Total	18
<hr/>	

TABLE 3.11

Abnormalities found during attacks in patients with
normal basic EEGs

<u>Abnormality found</u> <u>during attack</u>	<u>Number of patients</u>
Spike and wave	4
Slow or sharp activity with focal onset on right	4
Slow or sharp activity with focal onset on left	2
<hr/>	
Total	10
<hr/>	

TABLE 3.12

hyperventilation during the basic EEG, the records were examined to see if this had been performed.

It was found that overbreathing had been adequately carried out by all 4 subjects.

In order to assess how well the basic EEG would predict the type of seizure later recorded, the abnormalities found in the basic were compared to those found in the ambulatory record during attacks. Table 3.13 shows patients who experienced generalised EEG changes during attacks. The criterion for a generalised EEG change on a 3 channel recording was abnormality appearing clearly simultaneously in all 3 channels. It can be seen that the basic EEG proved most often to show generalised abnormality (spike and wave activity) or was normal. In two patients the basic EEG was misleading, showing unilateral abnormality.

Patients who experienced seizures showing partial EEG changes (ie. abnormality beginning clearly in one channel or one hemisphere) only occasionally showed unilateral abnormalities in the basic, as can be seen in Tables 3.14 and 3.15. Finally, patients whose EEG changes during attacks could not be classified are shown in Table 3.16, all of these patients showed abnormal basic EEGs.

Basic EEG findings in patients with generalised abnormalities during seizures in the ambulatory recording

<u>Basic EEG</u>	<u>Number of Patients</u>
Normal	4
Spike and wave	5 (2 photosensitive)
Unilateral slow or sharp	2 (1 right, 1 left)
Bilateral slow or sharp	2
Too slow for age	1
Tonic-clonic seizure	1
<hr/>	
Total	15
<hr/>	

TABLE 3.13

Basic EEG findings in patients with seizures which showed right sided EEG exacerberation during ambulatory recording

<u>Basic EEG</u>	<u>Number of Patients</u>
Normal	4
Unilateral slow or sharp on right	3
Bilateral slow or sharp	3
Too slow for age	4
<hr/>	
Total	14
<hr/>	

TABLE 3.14

TABLE 3.15

Basic EEG findings in patients with seizures
which showed left sided EEG exacerbation during
ambulatory recording

<u>Basic EEG</u>	<u>Number of Patients</u>
Normal	2
Unilateral slow on left	1
Bilateral slow	1
<hr/>	
Total	4

TABLE 3.16

Basic EEG findings in patients whose EEG changes during attacks were regarded as unclassifiable

<u>Basic EEG</u>	<u>Number of Patients</u>
Spike and Wave	2
Bilateral slow	1
Unilateral slow worse left	1
Unilateral slow and sharp wave worse right	1
Too slow for age	2
<hr/>	
Total	7

Basic EEG recording compared to ambulatory recording
in the diagnosis of sub-clinical discharges

Thirty five investigations were carried out to detect sub-clinical spike and wave discharges. All patients were receiving anticonvulsant medication and the aim of the investigation was to ensure that this was effective. Unfortunately, only 15 patients could be included in Table 3.17 because in the others, anticonvulsant medication was altered between the recording of the basic EEG and the ambulatory EEG.

Results show that in most patients spike and wave was present during both investigations. In one patient however, the basic EEG was normal and the ambulatory EEG showed spike and wave, and in one the basic was abnormal but did not show spike and wave activity but the ambulatory EEG did. Thus, in 2 patients the basic EEG failed to reveal sub-clinical discharges. In both of these patients hyperventilation was performed during the basic recording.

Anticonvulsant medication in patients whose attacks
showed no abnormality

It was hoped that the number of patients who showed no abnormality during attacks but were receiving anticonvulsant medication would provide a guide as to the

TABLE 3.17

Comparison between the basic EEG and the ambulatory EEG in patients referred for the detection of sub-

clinical discharges

	<u>Basic EEG</u>			Total
	Normal	Spike and Wave	Other	
Ambulatory EEG showed spike and wave	1	8	1*	10
Ambulatory EEG did not show spike and wave	3	0	2+	5
+ 1 patient unilateral slow right				
1 patient too slow for age				
* 1 patient too slow for age				

number who had been mistakenly diagnosed. However, two factors must be borne in mind when examining these figures. Firstly, some patients may have required medication for genuine seizure disorders which were well controlled but they continued to exhibit non-genuine attacks. Secondly, lack of scalp representation, particularly on the 3 channel recorder may have precluded the recording of EEG events. With regard to the first problem, it is however notable that 7 patients were actually suspected of having both genuine and non-genuine attacks, three of these patients experienced more than one attack during the recording but none showed a mixture of attacks with and without EEG abnormalities.

Table 3.18 shows that many patients in fact were not receiving treatment. Nineteen patients (28%) were receiving more than one anticonvulsant drug (AED) and 20 (30%) were receiving one AED alone or one AED plus benzodiazepines. Thus a possible 58% of patients were being treated unnecessarily.

Clinical description of attacks

The descriptions of attacks given by patients and observers were examined in order to assess whether there were any differences between attacks which showed no EEG change and those which did. Results are shown in Table 3.19.

Jerking, twitching, shaking or trembling was the most

TABLE 3.18

Details of medication in patients who showed
no EEG abnormality during attacks n = 67

<u>Medication</u>	<u>Number of Patients</u>	
Nil	25	(37.31%)
One AED	16	(23.88%)
More than one AED	16	(23.88%)
One AED + benzodiazepine	4	(5.97%)
More than one AED + benzo- diazepine	3	(4.48%)
Benzodiazepine alone	3	(4.48%)

AED = sodium valproate, carbamazepine, ethosuximide,
diphenylhydantoin, phenobarbitone, clonazepam,
clobazam

Benzodiazepine = lorazepam, temazepam, diazepam, nitrazepam,
clorazepate, chlordiazepoxide

Nil = No medication or specific medication only for non-epileptic
conditions

TABLE 3.19

CHARACTERISTIC FEATURES OF ATTACKS n=107

	EEG Abnormal n=40	EEG not Abnormal Possible simple-partial n=7 (aurs)	EEG not Abnormal n=67
Twitching, trembling, shaking, jerking	13	0	15
Focal Motor	6	0	4
Bilateral arms or legs	1	0	6
Stiffening, rigidity, tension	9	0	7
Salivation	2	0	1
Loss of consciousness, switches off, goes blank	6	0	9
Fall	4	0	5
Incontinence	1	0	2
Vague, thick/light headed, dizzy	3	2	10

TABLE 3.19 continued

	EEG Abnormal n=40	EEG not Abnormal Possible simple-partial n=7	EEG not Abnormal n=67
As if asleep	0	0	3
Change in respiration	2	0	0
Prolonged attack	1	0	3
Eye movements	4	0	5
Injury	0	0	5
Facial change	1	0	3
Pallor	0	0	2
Aggression	1	0	1
Automatisms	9	0	5
Sensory disturbances	2	2	9
Emotional disturbances	3	0	3
Head or stomach pain	2	2	6
Speech disturbance	9	0	5
Hot, cold, perspiring	0	0	5

TABLE 3.19 continued

	EEG Abnormal n=40	EEG not Abnormal Possible simple -partial n=7	EEG not Abnormal n=67
Giggling	1	1	2
Talking in sleep	0	0	1
Immobility	0	0	1
No description	5	0	4

common feature of attacks in both groups. Stiffening, rigidity, or tension was also seen quite often. Focal motor symptoms, ie. unilateral movement of limbs was present in a total of 10 patients, but in a further 6 who showed no EEG change there was bilateral jerking of either arms or legs alone, whereas only one patient with EEG abnormality showed bilateral jerking of upper or lower limbs separately.

Loss of consciousness or awareness was common in both groups particularly those who showed no EEG change. A feeling of vagueness or dizziness was also more common in the non-epileptic group. Surprisingly, 5 of these patients actually reported injuring themselves during attacks whereas none of those with genuine discharges injured themselves.

Automatisms occurred more often in those with abnormal EEGs during attacks and so did speech disturbances. Sensory disturbances such as tingling sensations, visual disturbances and 'funny feelings' were more often a feature of attacks which showed no abnormality as were head or stomach pains, and a change in body temperature and/or perspiring. A total of nine attacks were unobserved and no description was available other than the EEG change.

Due to the possibility of lack of scalp representation of simple partial seizures the number of attacks consisting of auras alone were investigated. Seven such attacks

were found to exist in the group which showed no EEG change.

Value of the ambulatory EEG in patients who did not experience attacks

Fifteen investigations (on 14 patients) showed abnormalities which were either not present or not as clear in the basic EEG even though no attacks occurred during the ambulatory EEG. Details of these abnormalities can be seen in Table 3.20. Nine patients showed focal sharp waves during sleep. When the basic EEGs of these nine were examined, 3 were normal, 3 showed benign rolandic spikes which became more obvious during sleep, one showed a focal abnormality during the basic on the opposite side to that found during the ambulatory sleep record, one showed generalised paroxysms in the basic and one showed focal slow activity without spiking.

Three patients showed spike and wave activity in the ambulatory sleep record, two of these had normal basic waking EEGs and one who, showed paroxysmal spike and wave in the basic, showed continuous spike and wave in the ambulatory sleep EEG. In one patient the sleep record was unusual showing extremely abundant, high amplitude vertex sharp waves. Finally, one patient did not experience typical attacks but 'funny feelings' which proved to be accompanied by spike and wave activity.

TABLE 3.20

Abnormalities found in ambulatory EEG in
patients who did not experience attacks

<u>EEG</u> *	<u>Number of Patients</u>
Focal sharp activity in sleep	9 (+ 1 repeat)
Spike and wave in sleep	3
Sleep unusual	1
Atypical attack accompanied by spike and wave	1
Total	15

* These abnormalities were not present or not as clear
in the basic EEG

Comparison of children and adults

Of the 215 recordings examined, 107 included attacks which were interpretable. Of these patients, 46 were over 21 years of age and 61 were less than 21 years. The type of EEG change associated with attacks was examined for each of the two groups (Table 3.21).

Results showed that in adults, 36 of a total of 46 patients showed no abnormality (78.2%). In children under the age of 21 years only 31 out of 61 showed no abnormality (50.8%). Thus unexplained attacks in children produced positive evidence for epilepsy in 49% of cases whereas in adults only 22% showed positive evidence of epilepsy.

The type of genuine seizures were compared for children and adults (Table 3.22). In adults the most common attacks were partial seizures with right sided predominance. In children absence seizures were equally as likely to occur as partial seizures. A number of attacks, mainly in children, were unclassifiable.

TABLE 3.21

DIFFERENCES BETWEEN CHILDREN (UNDER 21 YEARS)
AND ADULTS AT THE TIME OF ATTACKS

EEG During Attack

	<u>Abnormal</u>	<u>No change</u>	<u>Total</u>
Over 2lyrs	10	36	46
Under 2lyrs	30	31	61
Total	40	67	107

TABLE 3.22

TYPES OF GENUINE SEIZURES RECORDED IN
CHILDREN AND ADULTS

<u>Attacks</u>	<u>Over 21 years</u>	<u>Under 21 years</u>
Absence	1	9
Tonic-clonic	1	2
Myoclonic	1	1
R.partial	5	9
L.partial	1	3
unclassified	1	6
Total	10	30

A preliminary follow-up study

A small group of patients under the age of 21 years were chosen for follow-up. This group included 14 patients who were receiving AEDs at the time of the ambulatory recording and showed no EEG change at the time of recorded attacks. Four patients were receiving one AED, 7 two AEDs and 3 one AED and a benzodiazepine. Two of these had a definite history of epilepsy as well as the episodic symptoms under investigation.

Referring consultants were contacted by post and asked whether, at the last consultation, the patient was still receiving medication, whether attacks were still occurring and what was the final diagnosis? Results are shown in Table 3.23.

Six patients were no longer receiving AEDs and in 5 attacks had ceased. In one the consultant was not sure whether all attacks had ceased, but he was convinced that they were psychological in nature.

In 4 patients the final diagnosis was epilepsy. All were still receiving AEDs and 3 were still experiencing attacks. These patients were therefore examined in more detail as the ambulatory EEG at the time of the attack had shown no abnormality. Findings suggested that in one patient there was no loss of awareness, suggesting a simple partial seizure which might show

TABLE 3.23

RESULTS OF PRELIMINARY FOLLOW UP STUDY IN 14 PATIENTS WHO HAD BEEN
RECEIVING MEDICATION AT THE TIME OF THE AMBULATORY EEG AND SHOWED
NO EEG CHANGE DURING RECORDED ATTACKS

Patient	AEDS	Attacks	Final Diagnosis	Follow up (months)
1	-	-	reaction to events	22
2	-	-	emotional	60
3	-	-	night terrors	14
4	-	-	developed schizophrenia	57
5	-	-	emotional	19
6	-	?	psychological	12
7	+	+	epilepsy	48
8*	+	+	partial seizures	16
9	+	+	epilepsy	24
10	+	-	epilepsy	42
11**	+	-	panic	22

TABLE 3.23
(cont'd)

<u>Patient</u>	<u>AEDS</u>	<u>Attacks</u>	<u>Final Diagnosis</u>	<u>Follow up (months)</u>
12**	+	+	psychological	24
13	lost to follow-up			
14	lost to follow-up			
			Mean	30
			S.D	17

* = recorded attack showed no loss of awareness
 ** = patient had a definite history of epilepsy as well as the episodes under investigation

no EEG change (Ives and Woods 1929). In two patients (7 and 9) current attacks differ clinically to those which were previously recorded on the ambulatory EEG. In patient 10, all attacks had ceased whilst on AEDs and were therefore assumed to be epileptic.

Two patients had a definite history of epilepsy as well as the episodic symptoms under investigation and so these two were still receiving AEDs. Attacks ceased in only one of the patients but in both there was no doubt from the consultant that attacks were of psychological nature. Unfortunately, two final patients were lost to follow-up.

Follow-up ranged from 12 to 60 months, mean 30 ± 17 months.

Value of the 8 channel ambulatory sleep record compared to the basic EEG, in diagnosing attacks

It was not possible to carry out daytime sleep recordings in the laboratory due to the general level of noise in the department. It was hoped therefore, that in the future 8 channel ambulatory sleep recording might provide an alternative method of diagnosis in patients who showed no basic waking abnormality and had too few attacks to be recorded.

Before this was recommended however, the sleep record of patients already recorded and who had experienced attacks

was examined and compared also to the basic waking EEG. The aim of this investigation was to assess the validity of the sleep ambulatory EEG and compare it to that of the basic EEG.

In 8 patients whose attacks showed no EEG changes (Table 3.24) the basic waking EEG and the sleep EEG were normal. However, in just under half, the basic was abnormal whereas the sleep EEG was normal.

Thus, in these patients it would appear that the sleep EEG was less likely to produce false positive results. One of the patients whose basic and sleep EEG were abnormal had epilepsy as well as the attacks in question.

In patients whose attacks were epileptic (Table 3.25) all except for 2 showed abnormality in both the basic EEG and the sleep EEG. This number also includes 2 patients who experienced attacks in sleep. Thus, in patients whose attacks were genuine it was likely that both the basic and the sleep EEG would show abnormality.

Overall therefore, it would appear that in patients with genuine seizures both the basic and the sleep EEG will be abnormal in over 80% of cases. In patients whose attacks are not epileptic the sleep EEG may provide more reliable information than the waking EEG.

TABLE 3.24

AMBULATORY SLEEP EEG IN
PATIENTS WHOSE ATTACKS SHOWED NO ABNORMALITY

(8 CHANNEL RECORDINGS ONLY n = 17)

		<u>Ambulatory Sleep EEG</u>		
		<u>Normal</u>	<u>Abnormal</u>	<u>Total</u>
Basic EEG	Normal	8	0	8
	Abnormal	7	2*	9

* one patient with epilepsy also

TABLE 3.25

AMBULATORY SLEEP EEG IN
PATIENTS WHOSE ATTACKS SHOWED ABNORMALITY

(8 CHANNEL RECORDINGS ONLY n = 12)

		<u>Ambulatory Sleep EEG</u>		
		<u>Normal</u>	<u>Abnormal</u>	<u>Total</u>
Basic EEG	Normal	1	1*	2
	Abnormal	0	10*	10

* including 3 attacks in sleep

Examples of recorded attacks

Figures 3.36 to 3.50 show some of the attacks which were recorded. The timing shown, starts from the beginning of abnormality in the EEG. The first 6 attacks were predominantly right sided.

The attack shown in Figure 3.36 was possibly a simple partial seizure. The patient was aware of a pain in his stomach and a burning sensation in his mouth. Muscle activity may reflect mouth movement due to the taste. The classical pattern of incrementing sharp waves and spikes eventually gives way to post-ictal delta waves on the right.

In the second attack shown (Figure 3.37) abnormality appears to have begun with slowing in the right posterior region which increases in frequency and spreads to other areas. The clinical description of the attack suggested secondary generalisation.

Figure 3.38 shows an attack during which only very localised irregular slow activity was seen. Note the asymmetry in slowing which makes it unlikely to be eye movement artefact. Fortunately, several attacks were recorded which showed the same pattern and clarified the diagnosis. Symptoms of nausea were suggestive of a simple partial seizure.

In Figure 3.39 the event button is pressed prior to any

obvious abnormality which eventually appears initially in channels 1 and 5. After 28 seconds, abnormality is maximal in bilateral mid to posterior temporal regions but less marked anteriorly.

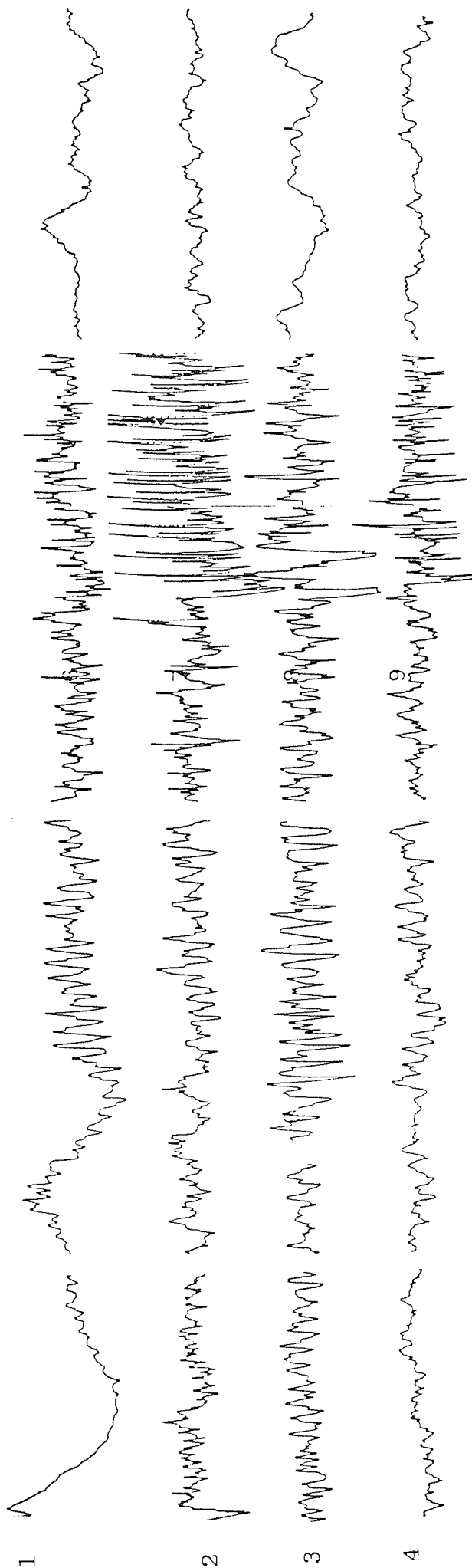
The following two attacks show more widespread changes. In Figure 3.40 the event button was pressed just prior to any abnormality. The attack shown in figure 3.41 probably became secondarily generalised. Abnormality clearly begins on the right and muscle activity is seen to be more pronounced on the left at the end of the attack.

In Figure 3.42 the onset of the attack is clearly left sided with little representation on the right. The following left sided attack^(3.43) also shows little spread to the right and surprisingly little abnormality in the left posterior temporal channel.

Figures 3.44 to 3.46 show some of the attacks which remained unclassified. In the attack in Figure 3.44 no clinical description was available as the attack occurred in sleep. This has the electrographic appearance of a tonic-clonic seizure but it is not entirely clear whether the onset was unilateral. There was a similar problem with the following attack although the clinical description was one of generalised jerking. The attack shown in Figure 3.46 may have been a tonic attack. The large artefact which is seen at the beginning is usually seen when patients fall, but in this case the onset of the attack was not observed.

Figures 3.47 and 3.48 show benign rolandic spiking in two patients during sleep. The standard 3 channel montage adequately recorded the abnormality but the 8 channel recording shows much better topographic detail.

Finally Figures 3.49 and 3.50 show the typical patterns encountered in pseudoseizures which mimic tonic-clonic attacks. In Figure 3.49 the event button is pressed and this is followed by a large artefact as the patient fell. Subsequent artefacts are sporadic and similar to those seen during tooth brushing and head shaking. At the end of the attack there is an immediate return of the alpha rhythm. In Figure 3.50 the alpha rhythm can be seen in-between bursts of artefact.



0

8

24

98

secs

D.G. AGE 27. PAIN IN STOMACH,
BURNING SENSATION
IN MOUTH

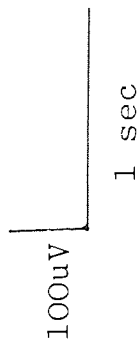
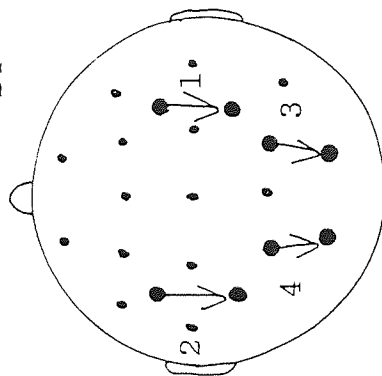
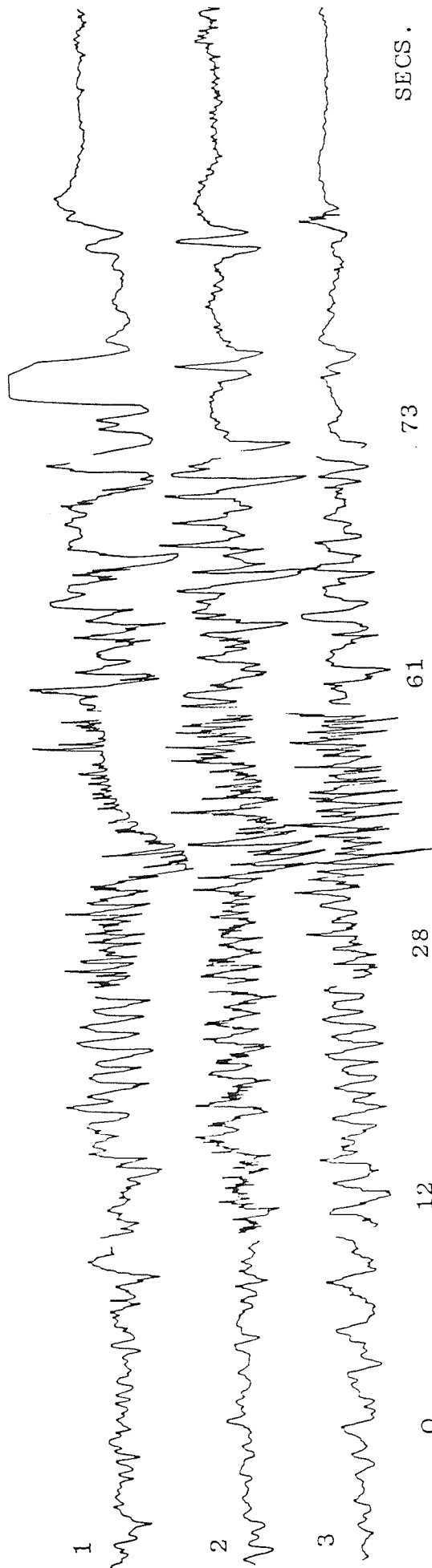
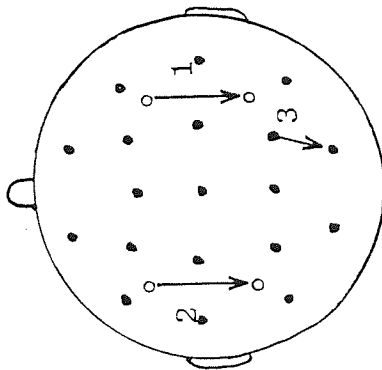


FIGURE 3.36 POSSIBLE SIMPLE PARTIAL SEIZURE SHOWING
ABNORMALITY BEGINNING ON THE RIGHT



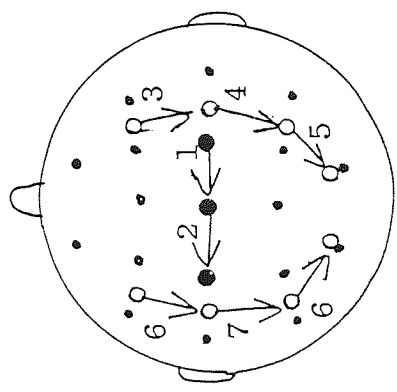
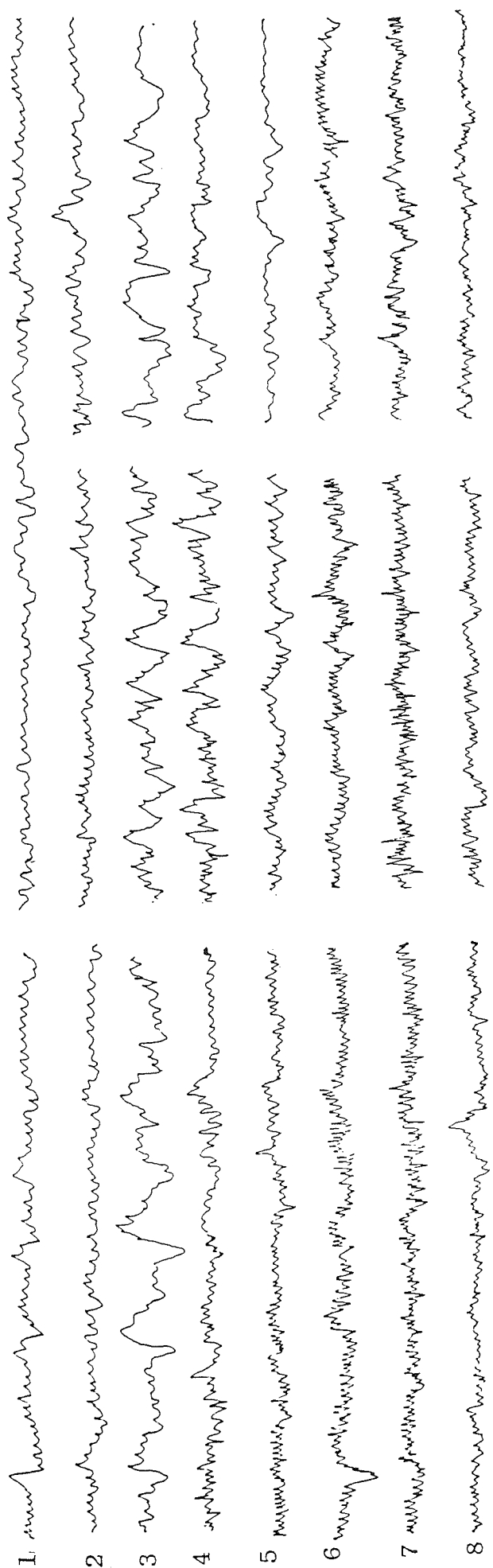
266

100uV
1 SEC.



V.B. AGE 18.
PRESSING HEAD INTO PILLOW,
JERKING, SALIVATING, HEAD
TWISTED TO RIGHT.

FIGURE 3.37 PARTIAL SEIZURE SHOWING ABNORMALITY BEGINNING
IN RIGHT POSTERIOR REGION WITH POSSIBLE
SECONDARY GENERALISATION



100uV
1 sec

C.S AGE 27
FELT NAUSEOUS

FIGURE 3.38. PARTIAL SEIZURE SHOWING MINIMAL CHANGES IN RIGHT ANTERIOR AND MID TEMPORAL REGIONS

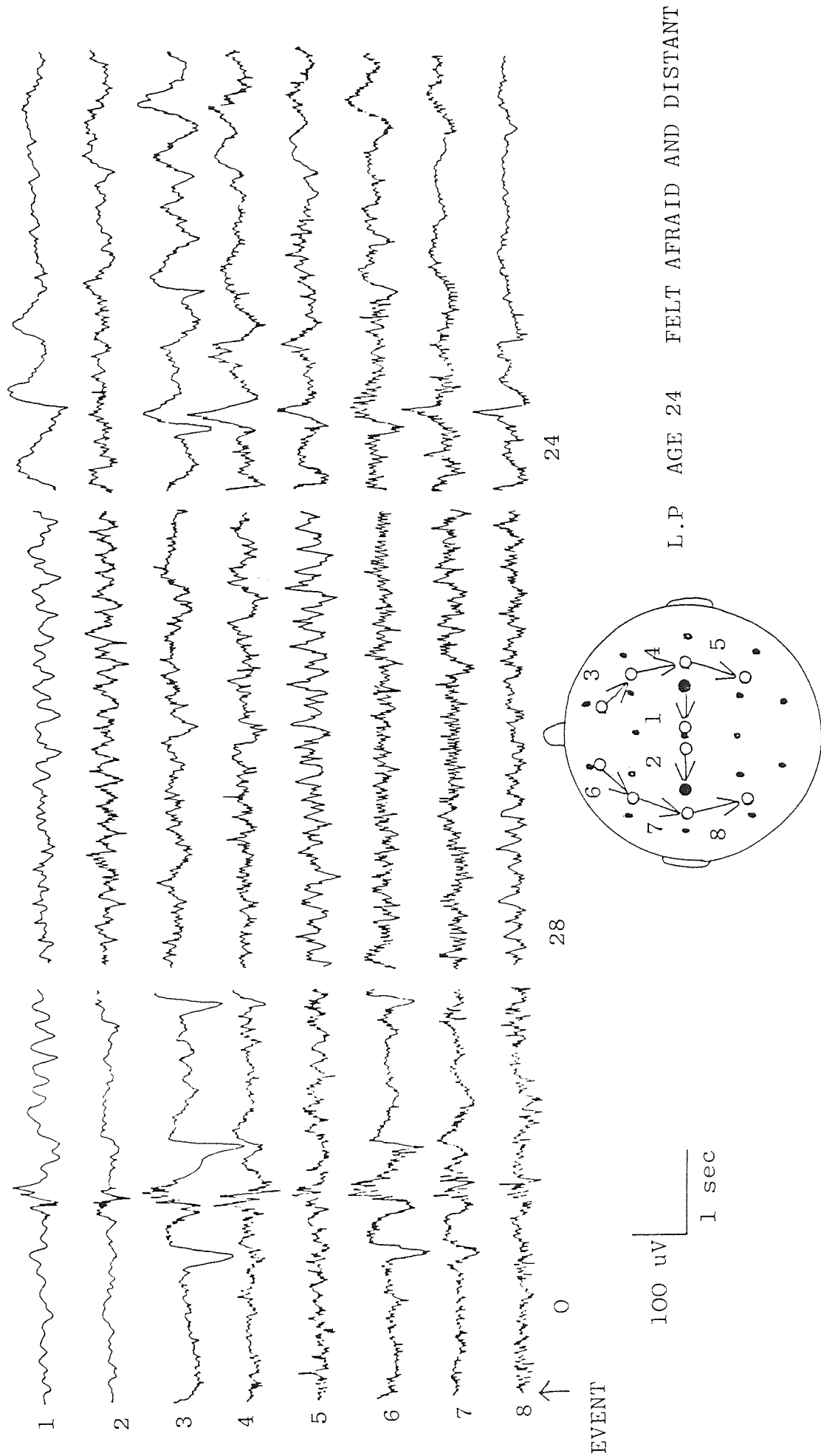
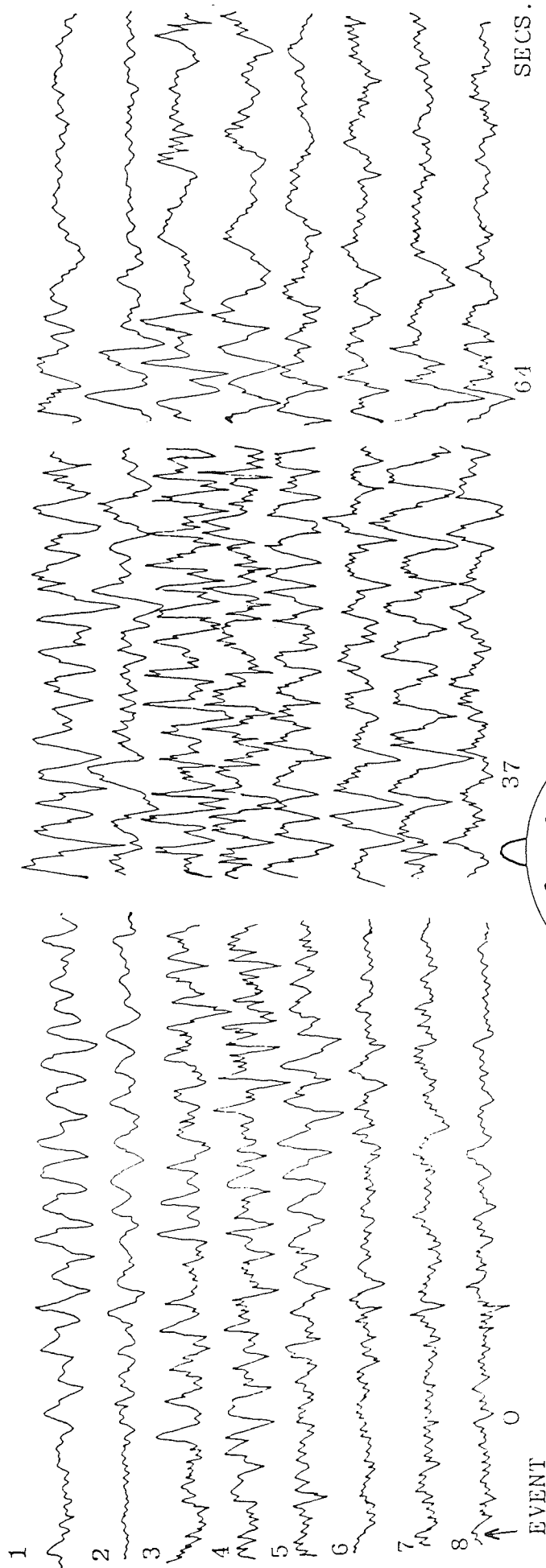
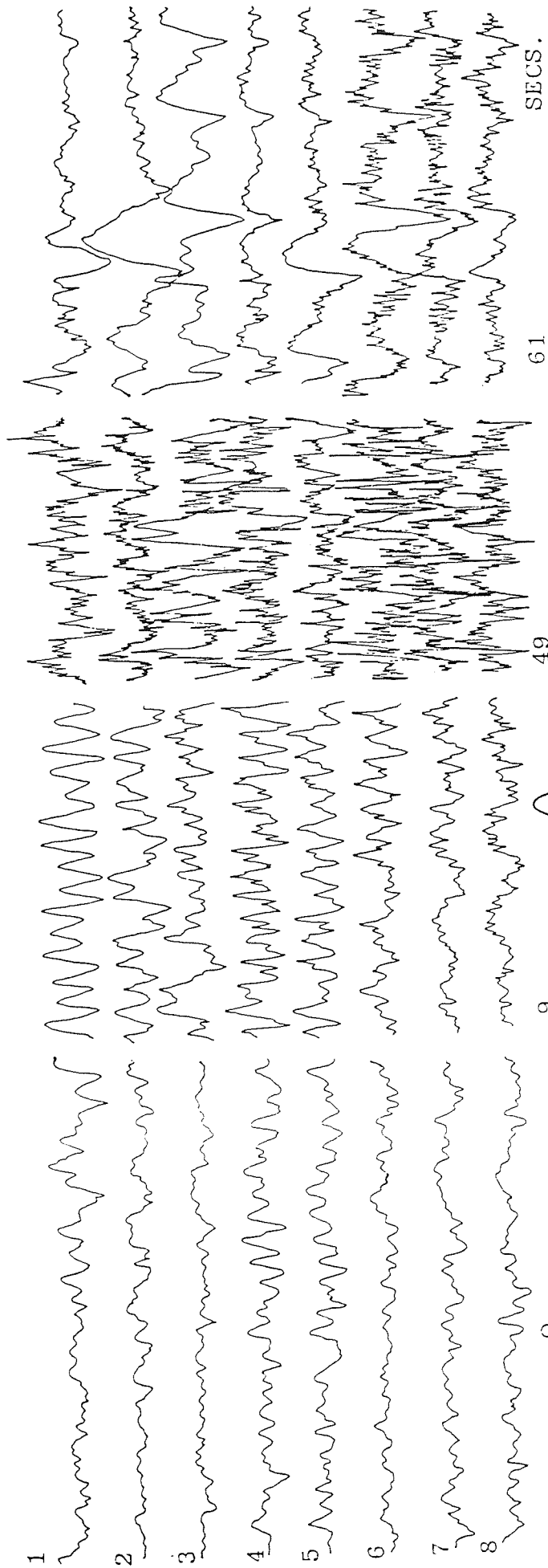


FIGURE 3.39 PARTIAL SEIZURE SHOWING ABNORMALITY BEGINNING IN RIGHT MID TEMPORAL REGIONS



J. L. AGED 26.
WENT BLANK, MUMBLED.

FIGURE 3.40 PARTIAL SEIZURE SHOWING ABNORMALITY BEGINNING ON RIGHT AND BECOMING WIDESPREAD



B. H. AGED 32.
HUSBAND WOKE, FOUND HER
LYING RIGID.

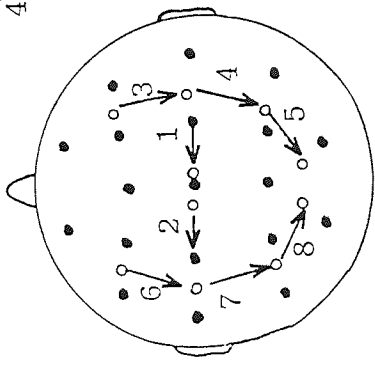


FIGURE 3.41 PARTIAL SEIZURE BEGINNING ON RIGHT WITH POSSIBLE SECONDARY GENERALISATION

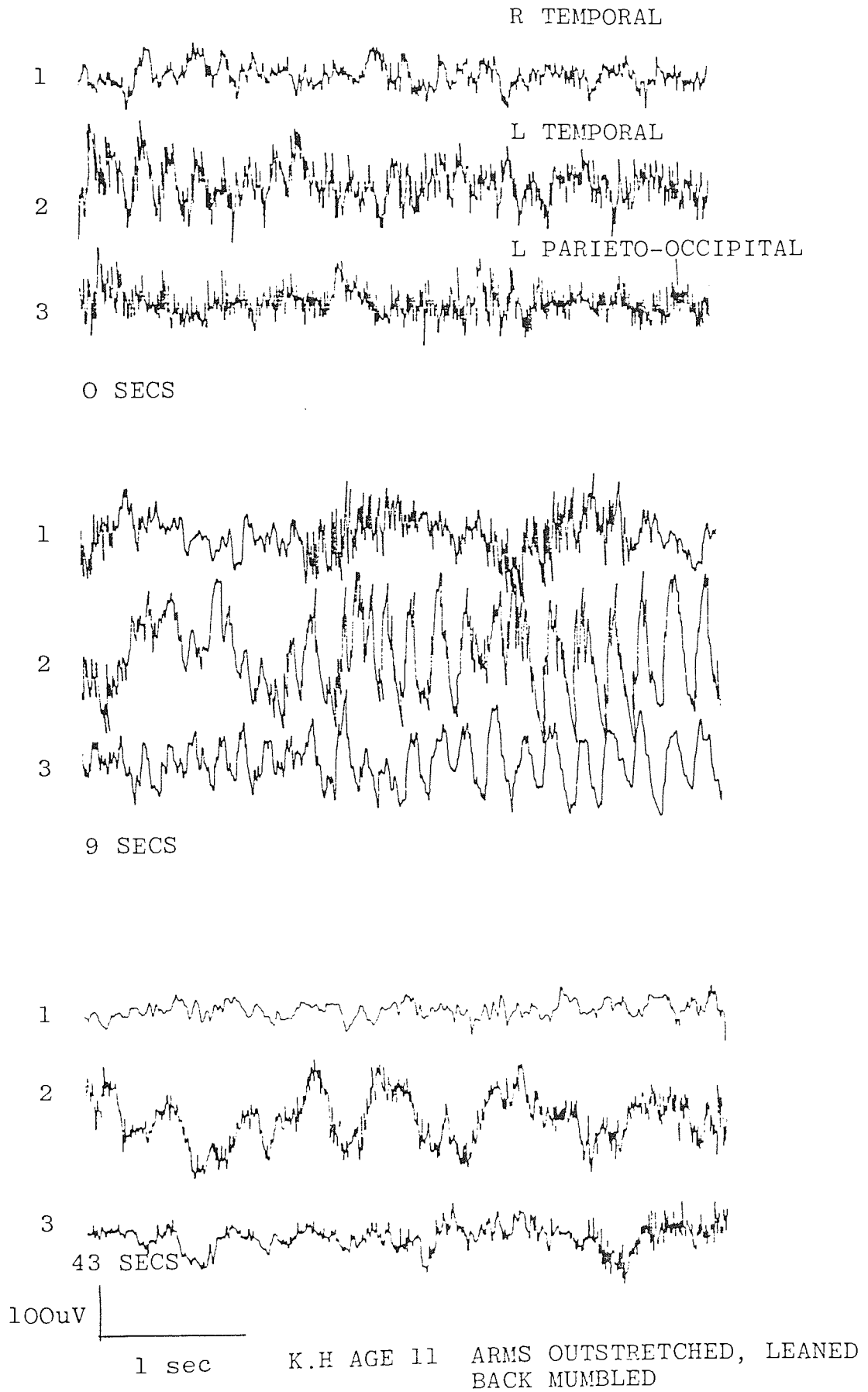
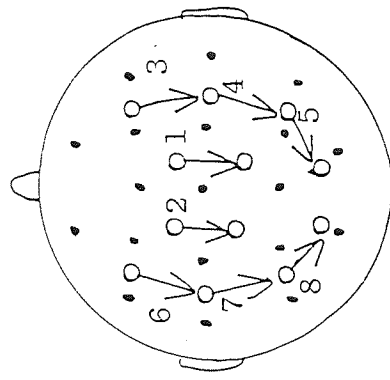
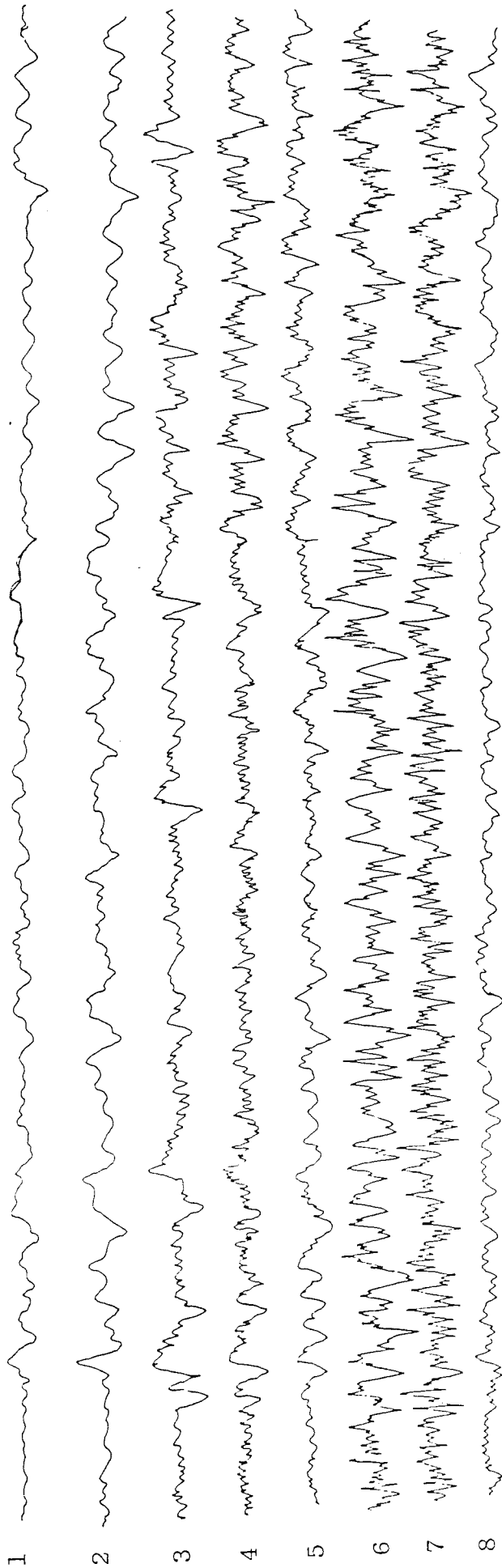


FIGURE 3.42 PARTIAL SEIZURE BEGINNING ON LEFT



100uV
1 sec

E.M AGE 30
SAT TAPPING MAGAZINE

FIGURE 3.43 PARTIAL SEIZURE SHOWING ABNORMALITY ON THE LEFT AND MINIMALLY ON THE RIGHT

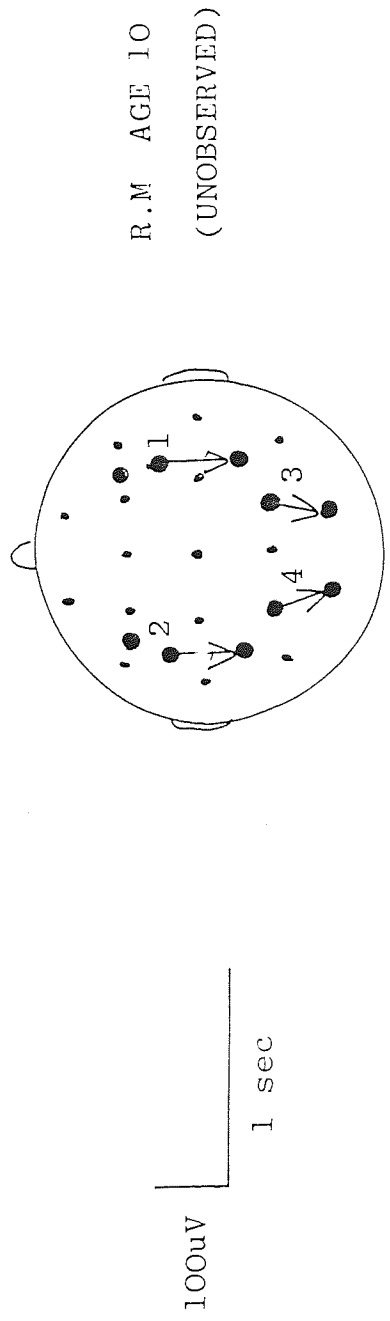
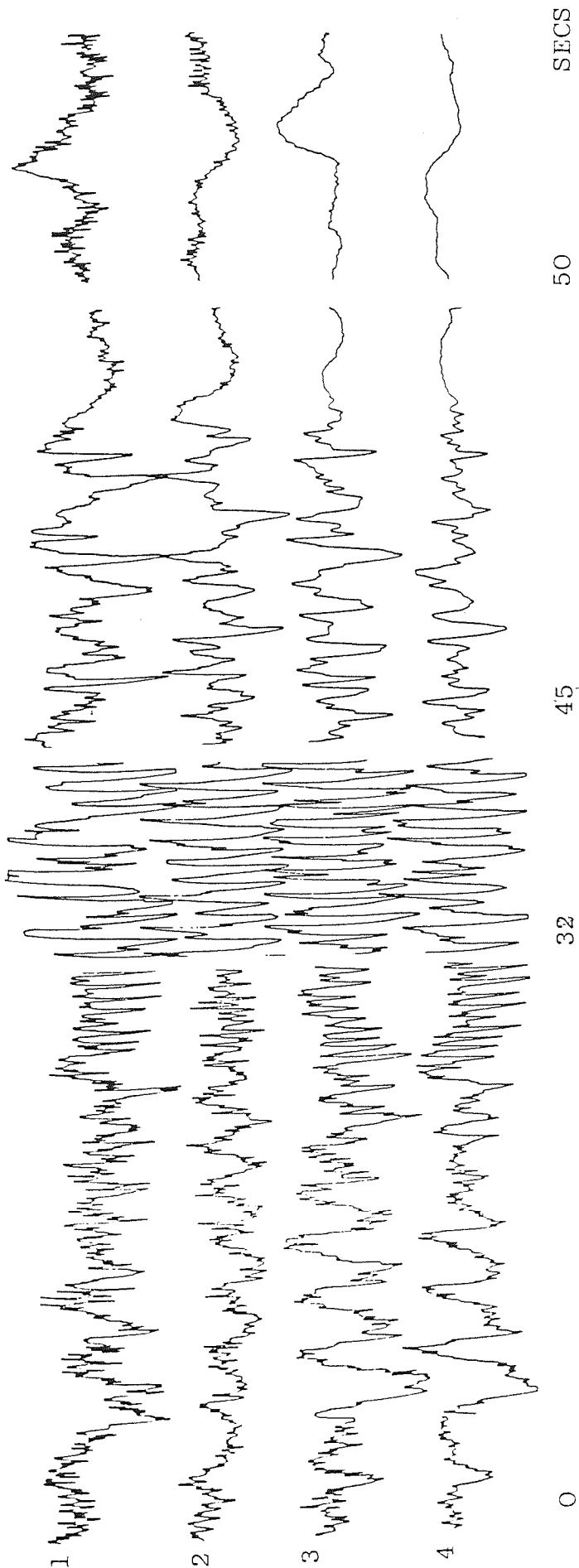
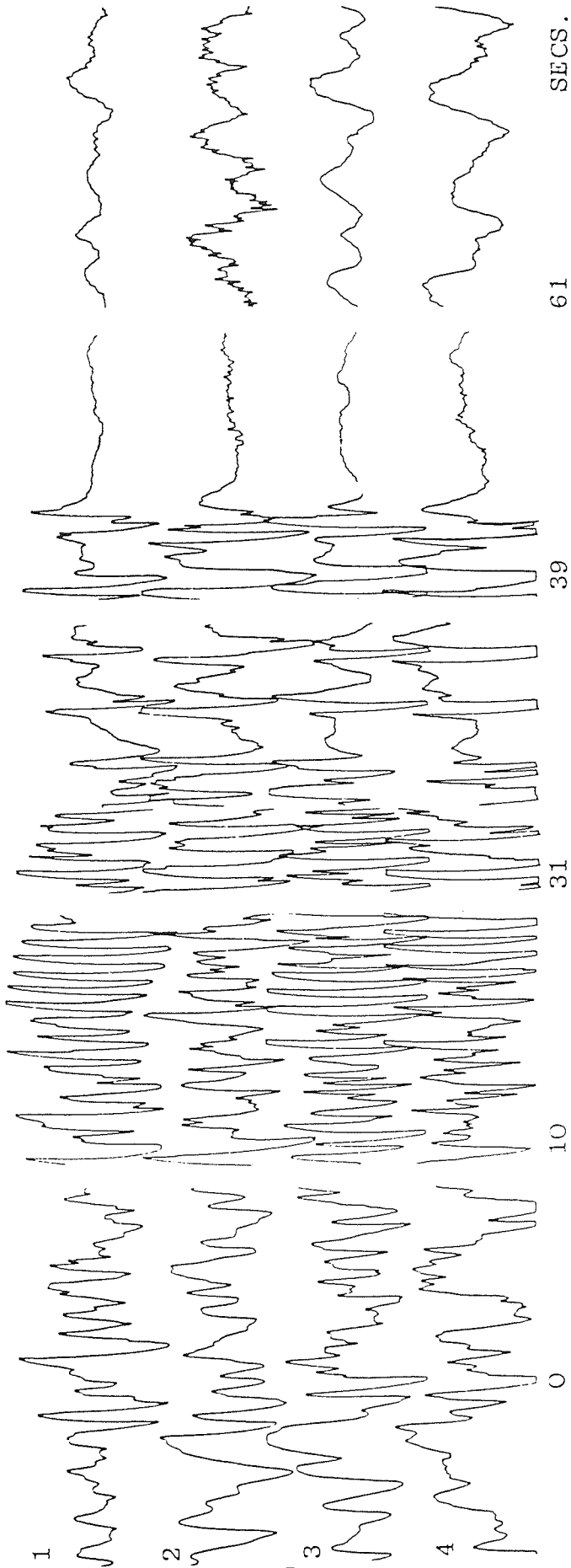
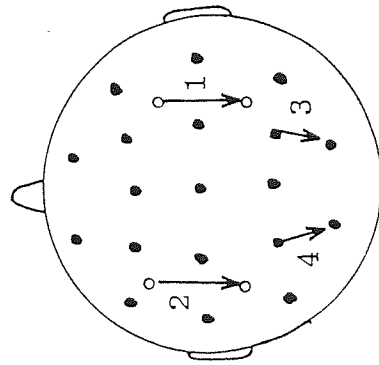


FIGURE 3.44 UNCLASSIFIED ATTACK DURING SLEEP

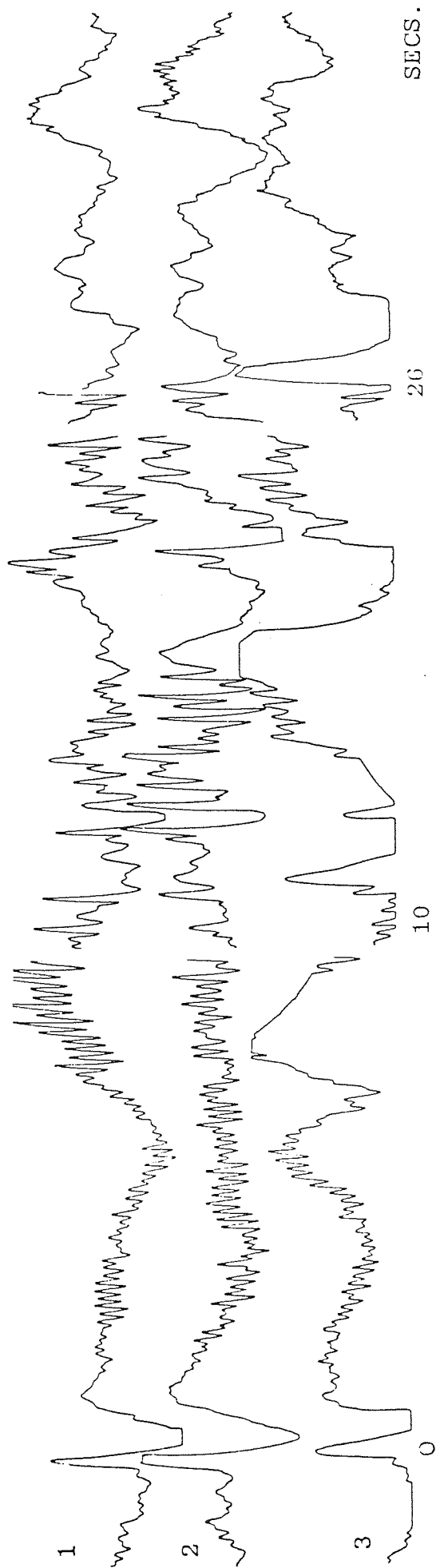


100uV |
1 SEC.



L.N. AGED 18 MONTHS.
JERKING ALL OVER.

FIGURE 3.45 UNCLASSIFIED GENERALISED ATTACK



R.C. AGED 8
RIGID, STARING.

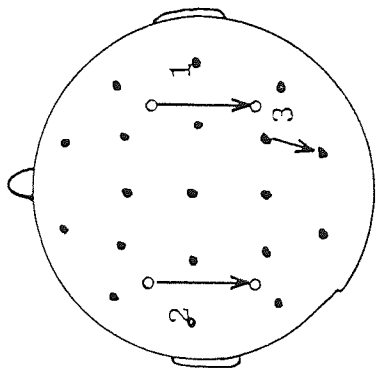
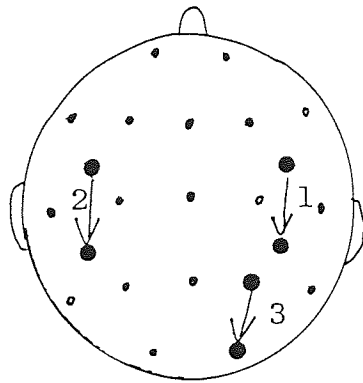
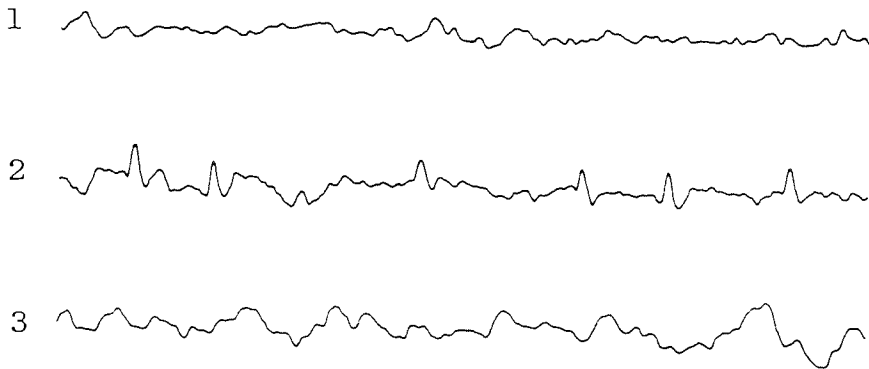


FIGURE 3.46 POSSIBLE TONIC ATTACK



100uV
1 sec

FIGURE 3.47 3 CHANNEL RECORDING OF BENIGN ROLANDIC SPIKING

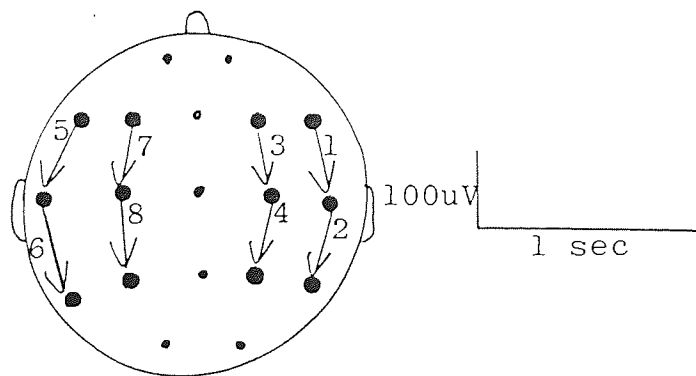
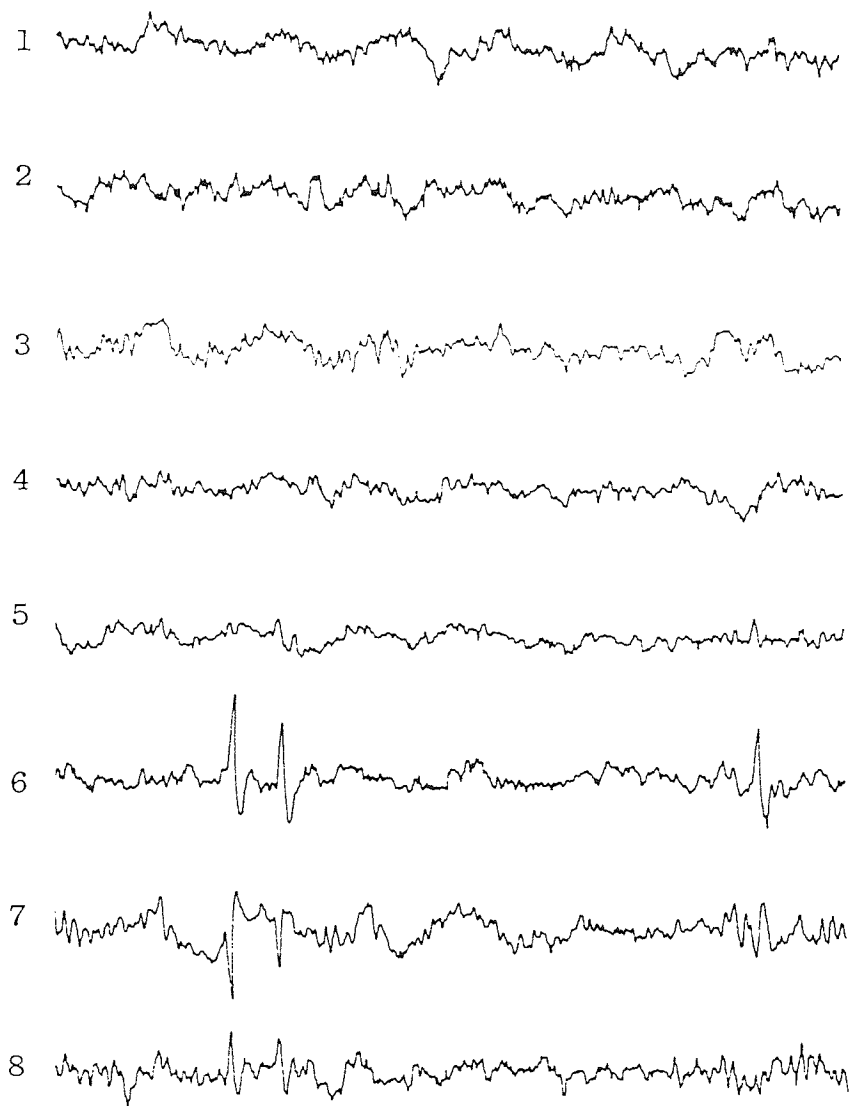
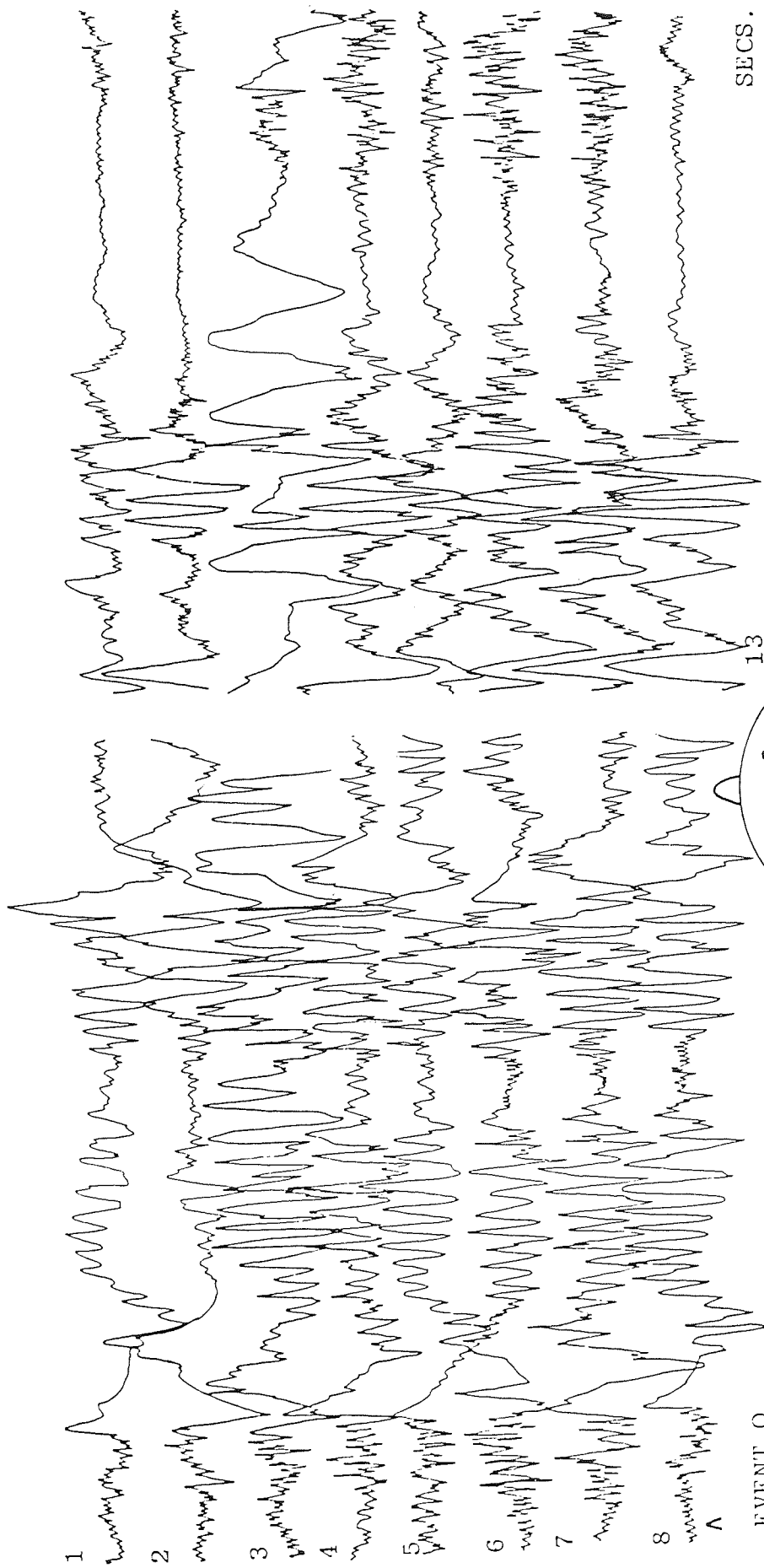
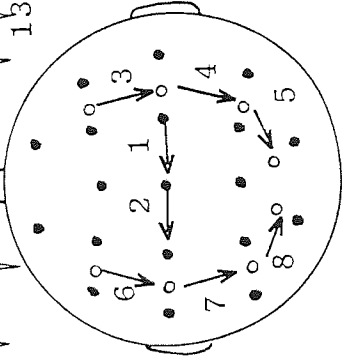


FIGURE 3.48 8 CHANNEL RECORDING OF BENIGN ROLANDIC SPIKING



SECS.

P. D. AGED 23.
 JERKING, SALIVATING,
 CLAWING AT RIGHT TEMPLE.



100uV
 1 SEC.

EVENT 0

FIGURE 3.49 PSEUDOSEIZURE BEGINNING WITH FALL

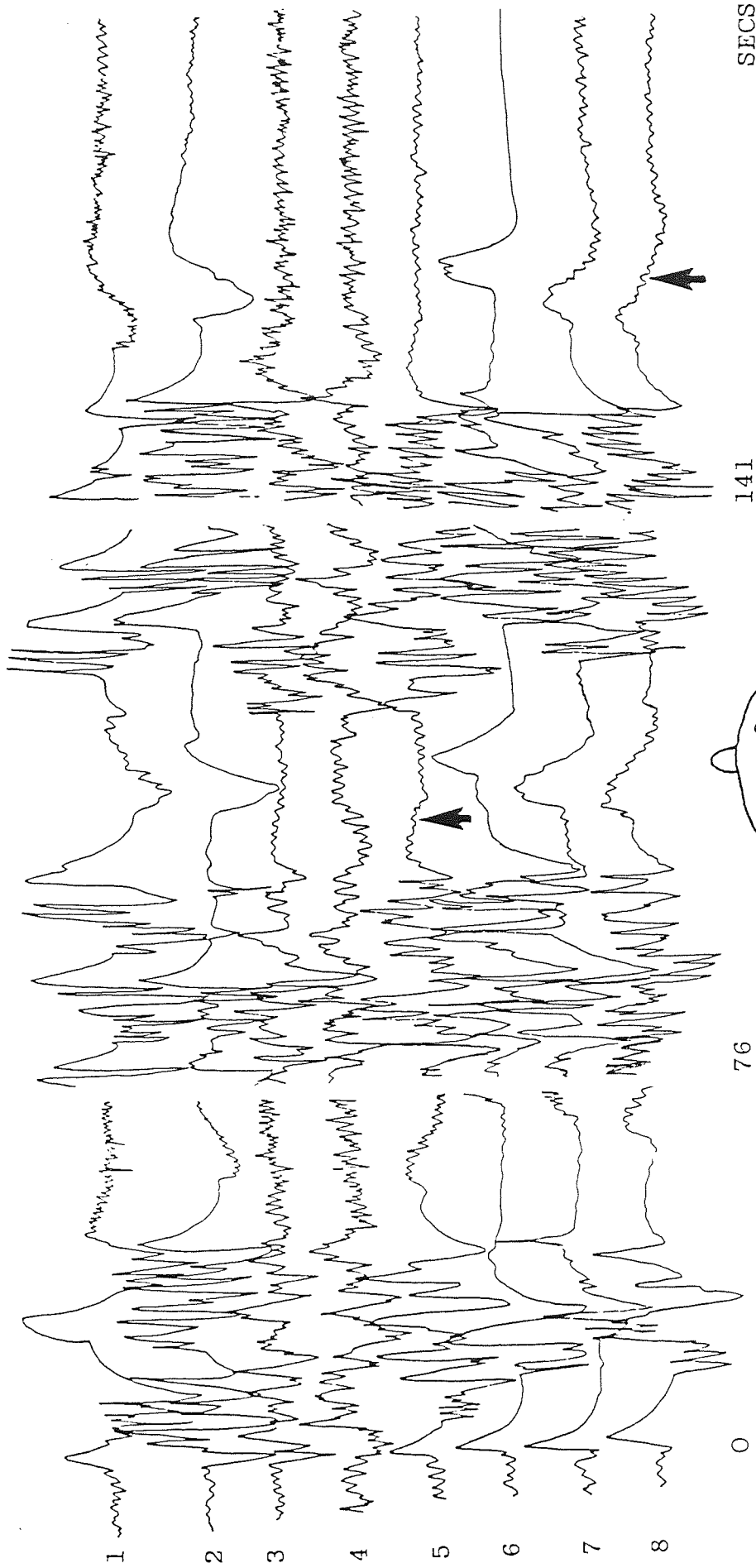


FIGURE 3.50 PSEUDOSEIZURE SHOWING ALPHA RHYTHM

Technical considerations

Although ambulatory monitoring is not inexpensive, the benefits to both the patient and the consultant are considerable and often outweigh the costs. These benefits however, depend on the correct utilization of the equipment, the maintenance of a high technical standard and careful interpretation of results. One of the first problems encountered concerned the differentiation of genuine abnormality from artefacts. Ambulant subjects produce a new range of artefacts which are never seen in the basic EEG, such as those arising from running, chewing and tooth-brushing. Therefore, recordings were made from several normal subjects in order to catalogue these artefacts and perfect the application technique. The morphology and distribution of artefact usually makes it distinguishable from genuine abnormality, however, when this is difficult the daily diary sheet which is kept by the patient proves invaluable.

There can still however, be considerable problems especially when muscle activity occurs at the time of attacks and obscures the EEG. There are several ways of minimising this. Firstly, careful montage design is necessary. Positions must include areas of the scalp most likely to show abnormality but also those least likely to produce artefact from jaw and eye movement. Leroy and Ebersole

(1983) showed that in adults the anterior temporal regions were more likely to show abnormality. In children, Klass (1975) suggests that the mid temporal and sylvian regions are more important. With these factors in mind, a montage was designed which includes temporal chains of electrodes which are slightly higher than the standard temporal positions but lower than the parasagittal. The 8 channel montage also included two central transverse channels. Secondly, the use of the 8 channel recorder enables wider coverage of areas of the scalp which are less likely to be obscured by artefacts during attacks. Fortunately, most complex partial seizures eventually show widespread EEG changes which can be seen in central regions as well as temporal regions (Klass 1975).

An adequate description of attacks can also help to explain some EEG findings. If the patient simulates an attack in the laboratory one can compare the kind of artefacts produced to those which occurred at the time of the attack. Close examination of the recorded attack is essential before the electrodes are removed. If the attack is totally obscured by artefact, recording should be continued and information gained from as many more attacks as possible. Even if the attack itself is obscured, post-ictal changes may be detected. Their absence however, cannot be assumed to indicate that attacks are not epileptic unless the description of the attack was suggestive of a tonic-clonic seizure. Escueta et al. (1977) found that in half of

their patients with partial seizures the EEG returned to normal whilst the patient was still confused and there are no post-ictal changes associated with absence seizures.

It is rare for all of these measures to fail so that attacks are uninterpretable. In the patients recorded, this occurred in only 6%. All of these had been carried out using 3 EEG channels. No such problems were encountered with 8 channels. Although Ebersole and Bridgers (1985) demonstrated that inter-ictal abnormalities were equally as well detected using 8 channels or 3, only 8 of their patients actually experienced attacks and therefore there were fewer problems with artefacts. When attacks are taken into account therefore, the 8 channel recorder is superior.

A figure of 6% for equivocal attacks is similar to most other authors, except for Blumhardt (1986) who found that 27% of attacks were uninterpretable. This author routinely uses two EEG channels and one ECG channel in all patients. Apart from Bachman (1984), who appears to find no problem with interpretation, Blumhardt is the only author to do this. Since we have demonstrated that 8 channels are superior to 3, it can only be assumed that the use of two EEG channels is a less effective recording technique.

Many authors have advocated the use of an ECG channel

when recording undiagnosed episodes of loss of consciousness. In the 4 patients in whom ECG was recorded in the present study, no useful results were obtained. Two patients did not experience attacks, one patient showed no EEG or ECG abnormality during an attack and in one patient the recorder malfunctioned. Similarly, of 113 patients who experienced attacks studied by other authors, only 8 showed cardiac abnormalities (Docherty 1981; Davidson et al. 1981; Blumhardt and Oozeer 1981; Callaghan and McCarthy 1982). In children, the incidence of ECG abnormality may be even lower than in adults (Green et al. 1984).

Three percent of investigations were technically inadequate, either due to recorder malfunction or patient interference. This is in keeping with most other authors whose failure rate in clinical patients range from 0.5 (Ives et al. 1976) to 8% (Stores 1980). Even under adverse conditions, such as during a military exercise, Abraham et al. (1977) only suffered a 15% failure rate. There was one unfortunate incident in which one patient failed to return to the laboratory and when the apparatus was finally retrieved it had been cut from the patient's head and an amplifier and all the electrodes were missing. In patients who are likely to damage the equipment it may be advisable to carry out 4 channel recording or to insist on hospital admission.

Selection of appropriate patients is crucial for the success of the technique. By allowing at least three days

for each patient and selecting only patients who have at least one attack per week, attacks were recorded in over 50% of investigations. This figure is similar to that of Forrest and Crawford (1981) who used a similar strategy. It is however, slightly lower than that of Davidson et al. (1981) who achieved a 77% success rate by recording only from patients who experienced more than one attack per day and recorded for one day only. According to Blumhardt and Oozeer (1981) lack of patient selection produces only a 16% success rate.

As previous authors (Sato et al. 1976) had suggested that the recording environment might affect the occurrence of attacks, investigations on patients recorded at home and those recorded in hospital were examined for any differences. There was a non-significant trend for patients who were recorded in hospital to be less likely to experience attacks. Riley, Porter, White and Penry (1981) also found that patients experienced fewer attacks in the first two weeks of hospital admission, than in the weeks prior to admission, despite medication remaining constant. Although unclear, the possible reasons suggested for this were, regular sleeping habits, low stress activities and the novelty of a different way of life.

Referral patterns

Three quarters of the referrals came in almost equal proportions, from psychiatrists, paediatricians and two consultants with a special interest in epilepsy. Only

14% of referrals were from neurologists. This may reflect a pattern of epilepsy referrals specific to our region; it would be interesting to find out the trends in other areas.

Seventy five percent of referrals were for patients with undiagnosed attacks. Investigations were therefore performed either to confirm or exclude a diagnosis of epilepsy. Most other authors have utilised the recorders in the same manner, eg. Stores (1985).

The next most frequent reason for recording was to assess the frequency of occurrence of absence seizures (14% of investigations). Several of these consisted of repeat investigations on the same patients after medication had been adjusted by the consultant.

Eleven patients (16 investigations) were referred for symptoms such as enuresis and sleepwalking, which occurred at night and were suggestive of nocturnal seizures. Five patients experienced attacks, only one of whom showed any EEG abnormality. One patient showed continual spike and wave activity in all stages of sleep except for REM, one patient showed occasional spike and wave discharges and one showed focal sharp waves. Thus in 8 of 11 patients referred specifically for sleep recording, this was useful.

Finally, 13% of investigations were carried out to clarify attacks. If a better description of the seizure type

can be gained this can help with the choice of treatment. There was a reluctance to use 3 channel recording to do this because of the lack of scalp coverage. As pointed out by Ives and Woods (1979), the positioning of the 3 channels immediately localises attacks to the chosen areas. It is possible to lateralise discharges if abnormality clearly predominates on one side. However, if all channels are positioned in the temporal regions and abnormality is bilateral, it may be difficult to decide whether attacks are generalised unless they show classical EEG changes such as spike and wave activity. Several of the attacks recorded on 3 or 4 channels therefore remained unclassified. Classification also obviously relies on a clear clinical description. Better localisation is however possible, using an 8 channel recorder and in 8 of our first 50 patients this was the reason for investigation. Four patients experienced attacks and a better description was obtained. Stores (1986) also found that in 20 of 23 patients in whom the basic and the sleep EEG were equivocal an 8 channel recording clarified the seizure type.

None of the patients in the present study were investigated as a work up to surgery. Although Ives and Woods (1979) have shown that 3 channel recording can provide a 'first look' at seizure discharges in surgical patients, it was always used in combination with other techniques.

Investigation of undiagnosed attacks

Three quarters of the patients referred for ambulatory monitoring had attacks of an uncertain nature. Investigations were therefore performed either to confirm or exclude a diagnosis of epilepsy. Of the recorded attacks 35% were accompanied by EEG abnormality and 59% were not. These figures are in agreement with other authors whose proportion of non-epileptic attacks ranged from 77% (Ives et al. 1981) to 27% (Callaghan and McCarthy 1982). Many of the former authors' patients however, had a firm clinical diagnosis of non-epileptic attacks and in the latter author's group, many had a clinical diagnosis of epilepsy.

Of the epileptic seizures which were recorded, partial seizures were the most common (45%). This is more than the 25% of all epilepsy referrals estimated by Currie et al. (1971). Because the symptomatology of partial seizures can be so diverse, they are more difficult to diagnose and therefore more often referred for ambulatory recording. It is also interesting that in our group there was a large bias towards attacks of right sided predominance, whereas Currie et al. found fewer right sided foci than left, and Ives and Woods (1979) found equal proportions. Gupta and Jeavons (1985) have reported that it is more difficult to obtain complete control of seizures in patients with right sided foci than in those with left foci. It is possible that a lack of control in these patients led to the doubt

about the diagnosis. Furthermore, patients with right sided foci often experience psychic auras (Gupta et al. 1983), which can be complex and may cast more doubt on the diagnosis.

Tonic-clonic seizures were recorded in 8% of patients, which is a slightly lower percentage than that estimated by Gastaut et al. (1975) for epilepsy sufferers as a whole.

Conversely, absence seizures were over-represented occurring in 25% of cases. This may have been because absence seizures tend to occur more often during a day and therefore were more likely to happen during recording. Patients therefore more often fell into the group who experienced attacks.

Sixty-seven patients showed no EEG abnormality during attacks.

On the basis of descriptions from patients and observers a comparison was made between the characteristics of these attacks and those of the genuine seizures. This was possible because observers had been closely questioned about the recorded attacks to aid EEG interpretation.

Jerking, twitching, shaking or trembling were common in both types of attack, as were stiffening and rigidity. However, jerking or shaking of the arms or legs alone, was found in 6 descriptions of non-epileptic attacks and only 1 genuine seizure. Scott (1982) has noted that during pseudoseizures jerking may occur randomly,

in different limbs and often switches from place to place. Feelings of light headedness, dizziness or fainting were also more common in non-epileptic attacks (10:3), as were sensory disturbances such as tingling sensations, funny feelings and visual distortions (9:2). Desai et al. (1982) have also commented that the onset of pseudoseizures tends to be gradual with prolonged non-specific warnings such as those described above. In genuine seizures however, the aura may only last for seconds.

A surprising finding was that 5 patients injured themselves during non-epileptic attacks. Self injury has been reported by other authors in pseudoseizures and should not be taken as an indication that attacks are epileptic (Liske and Forster 1964; Guberman 1982). Cohen and Suter (1982) found that 24% of patients with pseudoseizures reported tongue biting in the past. As pointed out by Parsonage (1973), teeth indentation marks are characteristically found down one side of the tongue after a tonic-clonic seizure. However, the tongue may be bitten at the tip during a fall (Jeavons 1983). In the present study injury may have been absent in genuine seizures because most of the recorded attacks were absences or partial seizures and there were few tonic-clonic attacks. In fact, only 9 patients actually experienced a fall.

There were 7 patients who experienced attacks during

which consciousness was not impaired. Symptoms consisted mainly of head or stomach pain, sensory disturbances and dizziness. The possibility that some of these attacks were genuine seizures but showed no scalp changes must be considered (Ives and Woods 1979; Klass 1975). The fact that in other patients the event button was pressed prior to any EEG change, also bears out this finding. Thus in such cases, where there are no EEG changes at the time of attacks it is impossible to make a firm diagnosis on the basis of the EEG.

Features which were more characteristic of epileptic attacks were automatisms and speech disturbance, incontinence was reported in one genuine seizure and two non-epileptic attacks. Incontinence should not be taken as an indication that attacks are epileptic. Cohen and Suter (1982) report that two patients were incontinent in the laboratory during pseudoseizures which had been provoked by suggestion. Incontinence is also quite common in syncopal attacks (Jeavons 1983).

Of the recorded attacks 40 patients showed EEG abnormality and 67 showed no changes. When age differences were examined this revealed an interesting finding. In patients under 21 years the EEG was abnormal during attacks in 50% of cases. Thus positive evidence for epilepsy was found in half of the children and young adults referred, but in less than a quarter of the older age group. These findings are in agreement with Green et al.

(1984) who found that in patients under the age of 20 years epilepsy was the most likely diagnosis.

To assess the number of patients who had been incorrectly diagnosed as epileptic, the medication being received by patients who showed no EEG abnormality during attacks was examined. These results require careful interpretation as it is difficult to be certain how many patients were being treated for definite seizures as well as the attacks in question. To our knowledge there were only three in this category. Other authors have shown that pseudoseizures are not necessarily more common in patients with epilepsy. Cohen and Suter (1982) found this in only 12% of patients and King et al. (1982) in only 25%. This is not to suggest however, that all of the non-epileptic attacks which were recorded were pseudoseizures. The data showed that 40% of patients were not being treated with AEDs, 25% were receiving one AED and 25% were receiving more than one AED. The use of polytherapy indicates the possible difficulty encountered in controlling attacks. In patients with pseudoseizures this may increase the number of attacks, as overdosing with AEDs can disinhibit the patient (Niedermeyer 1970).

The preliminary follow up study looked at the validity of ambulatory recording in such patients in greater depth. This was carried out on 12 patients under the age of 21 years who had shown no EEG abnormality during attacks and who were receiving medication at the time of

the recording. This group was chosen as comprising the most likely patients to have been wrongly diagnosed by the ambulatory EEG. The ambulatory EEG proved to be consistent with the final diagnosis in 8 of the 12 patients studied (67%). In 2 of the discordant patients recorded attacks differed to current attacks and one patient experienced a possible partial seizure without loss of awareness.

Two factors must therefore be taken into account when interpreting negative EEG results. Firstly, as previously stated, even on a 16 channel EEG, partial attacks without loss of awareness may show no changes or only very subtle changes at the scalp (Klass 1975). An 8 channel ambulatory EEG may not detect these changes and a 3 channel is even less likely to do so. It is extremely important therefore, before arriving at any conclusion, that an adequate description of attacks is obtained. Secondly, it is important to ensure that a typical attack has been recorded and if the patient has different types of attack, the recorded attack should be clarified in the report.

If these possibilities are accounted for, then it would appear that results of ambulatory monitoring are valid when compared to the clinical opinion. A similar observation was made by Oxley et al. (1981) who found that the ambulatory EEG agreed with the clinical opinion in 78% of cases, although this study included patients with a definite diagnosis and was not a follow up study.

Comparison with the basic EEG

If ambulatory monitoring is to be used in ordinary EEG departments then its superiority to the basic EEG must be proven. Results of the ambulatory EEG in the group of patients referred for attacks of an uncertain nature were therefore compared to the basic EEG findings.

In patients whose attacks showed no EEG change, the basic EEG was abnormal in 27%. In most, the abnormality was non-specific, but in 4 there was bilateral or unilateral slow or sharp waves. This is a higher incidence than that reported in the literature. Zivin and Ajmone Marsan (1968) in their review, estimate that spikes and sharp waves occur in 2% of patients with various other psychiatric or neurological conditions. Goodin and Aminoff (1984) found that 4% of a similar group of patients showed abnormality. In normal children, Turner (1982) and Ono, Mishima, Farukawa et al. (1980) showed that the incidence of spikes or spike and wave may be between 7 and 9% with hyperventilation and photic stimulation. Thus, the findings of the present study are atypical. As far as could be ascertained these patients did not have genuine seizures also. Many of the patients were however, psychiatric referrals and Stevens (1975) has suggested that patients with psychiatric disturbances show an increased incidence of temporal EEG abnormalities which may explain the reason for the findings.

Over 50% of the patients with epilepsy did show some

abnormality in the basic EEG (not including EEGs which were non-specifically slow). This is similar to the 52% obtained by Goodin and Aminoff (1984).

In 15 of the 75 patients (19%) who did not experience attacks the ambulatory recording showed abnormality which was not as clear or not present in the basic EEG. This is slightly higher than the 11% estimated by Ramsay (1981) for inter-ictal abnormalities. His patients however were not selected on the basis of frequency of attacks.

Overall, of the 215 investigations, interpretable attacks were recorded in 107. In a further 15 patients, additional abnormalities were found, making a total of 122 useful investigations or 57% of the total. In comparison, the basic EEG showed abnormality (other than non-specific slowing) in 18 patients and attacks were recorded in the laboratory in two patients making a total of 9%. If only focal abnormalities or spike and wave in the basic are included, then there were only 13 useful investigations (6%). Therefore, the ambulatory EEG provided 10 times as much information as the basic EEG.

The value of the sleep EEG in ambulatory monitoring

Korner et al. (1982) and Riley and Peterson (1983), showed that the quality of sleep obtained by subjects whilst wearing the ambulatory recorder at home, was better

than the sleep obtained in the laboratory. Present findings would support this view as few patients reported any difficulty in sleeping. In those who did, the sleep record did not bear out their claims. The main problem if any, seemed to be the noise of the recorder rather than the apparatus itself.

In our own laboratory sleep recordings are rarely performed due to ambient noise. The ambulatory recorder might therefore, be a useful alternative in patients whose attacks were not frequent enough to be recorded, but who might show EEG abnormality during sleep. As a guide to how useful such sleep recordings might be, the sleep records of patients who had experienced attacks in the past during 8 channel recording were examined.

Findings suggested that in patients whose attacks showed no EEG changes, the sleep record was less likely to produce a false positive result than the basic waking record. Five of the 7 abnormal basic EEGs, in fact showed non-specific slowing. In the patients with epilepsy, most showed abnormality in both the basic EEG and the sleep EEG. In only two of these however, was the basic EEG non-specific. Of these two patients, one showed spike and wave during sleep and one experienced an attack. (The high incidence of abnormal basic EEGs in this group was due to the inclusion of 4 patients who had been referred for differentiation of the seizure type).

There are too few patients and seizure types to allow

one to relate these sleep findings to the work of Janz (1974). However, there is some indication that the overnight sleep recording might clarify results in patients whose basic EEGs show non-specific slowing.

CHAPTER 4

THE USE OF SODIUM VALPROATE
IN THE TREATMENT OF EPILEPSY

4.1 A REVIEW OF SODIUM VALPROATE IN THE TREAT-
MENT OF EPILEPSY

Introduction

Dipropylacetic acid was first synthesised in 1881, and it was subsequently used as an organic solvent. In 1963 a group of workers in Grenoble (Meunier, Carraz and Meunier et al.) were testing an alkaloid called norkhelline for its pharmacological properties and found that it had an anticonvulsant effect on pentylene-*m*-trazol induced seizures in mice. The effects turned out to be due to the solvent used, which was dipropylacetic acid (Meijer and Meinardi 1976).

The sodium salt is marketed under the generic name sodium valproate and is known as; Depakine, Depakene, Eureka, Epilim, Ergenyl and Labazene. It has been used in France since 1967, the United Kingdom since 1972 and (as valproic acid) in the United States since 1978.

An extensive review of the literature up until 1975 is given by Simon and Penry (1975) including 13 clinical trials and several case reports. More recent literature is reviewed by Dulac and Arthuis (1984) and Gram and Bentsen (1984).

Sodium valproate in the treatment of generalised seizures

Simon and Penry (1975), after collating data from several different studies, ascertained that of a total of 218 patients with absence seizures 64% attained a reduction in seizures by more than 75%. In most cases however, valproate was added to existing medication and patients were those who had proven difficult to control.

Later studies have suggested that this figure may be even higher. Jeavons, Covanis, Gupta and Clark (1980) found that 87% of patients with absences were controlled on valproate alone or in combination with other AEDs. In general polytherapy was only required in patients with eyelid myoclonia who also received ethosuximide. It was also shown that absences alone or absences with automatisms respond equally well although some patients with a longer history of absences with automatisms (mean 11 years) required polytherapy. Jeavons (1983) found that 61% of patients on monotherapy with sodium valproate were free from absences.

The other drug of choice for absence seizures (except in combination with tonic-clonic seizures) is ethosuximide. Callaghan, O'Hare, O'Driscoll et al. (1982) carried out a comparative crossover study of ethosuximide and sodium valproate. Results showed no overall difference between

the two drugs. Two patients in each group failed to respond and all but one were crossed over and responded well. One patient did not respond to either drug or to a combination.

Martinovic (1983) carried out a similar study and achieved complete control in 15 of 20 patients without any difference in efficacy between the 2 drugs. He did find however, that the time taken to achieve complete control was longer in patients put on valproate (12 - 99 days, mean 45). Control was assessed on the basis of parental reports.

The success of sodium valproate in the treatment of atypical absence seizures is difficult to assess as there are often problems with classification. According to the 1981 classification, atypical absences would be those associated with Lennox-Gastaut syndrome. Jeavons and Clark (1974) found that all patients with spike and wave in the EEG responded. However, it would appear that these authors were referring to absences with automatisms. They refer separately to 11 patients with myoclonic astatic epilepsy who showed myoclonic jerks, eyelid flutter, astatic attacks and tonic-clonic seizures. They found that 6 showed more than a 50% improvement and several drugs had been tried unsuccessfully in each case. Simon and Penry (1975) refer to atypical absences simply as a "variant of petit mal" and estimate that of 67

patients in 7 studies (including Jeavons and Clark 1974), 48% of patients achieved more than a 74% reduction in seizures. Jeavons (1981) found however, that only 21% of patients with myoclonic astatic epilepsy were controlled on Epilim alone and Dulac and Arthuis (1984) note that only one of five patients benefited.

Jeavons (1982) reviews the response to treatment in patients with various types of myoclonic seizures. In infantile spasms he advocates that adrenocorticotrophic hormone should preferably be used, with benzodiazepines or valproate being used as maintenance therapy until 3 or 4 years of age.

Myoclonic epilepsy of childhood consisting of generalised jerks with 3 cps spike and wave is said to be controlled in 80% of patients using valproate alone. Jeavons (1982) notes that clonazepam is also effective but sedates.

Myoclonic epilepsy seen in adolescents which occur mainly on waking and are often accompanied by occasional tonic-clonic seizures, are said also to respond to valproate. In about half of these patients there is also photosensitivity.

The use of sodium valproate in photosensitive patients was reported by Jeavons, Maheshwari, Herrick and Harding (1976). These authors studied 37 patients who showed

a photoconvulsive response (P.C.R.) in the EEG on photic stimulation. On dosages ranging from 800 to 1200mg the P.C.R. was abolished in 18 patients and the upper and/or lower sensitivity range was reduced in most other patients. Jeavons and Harding (1975) found that many patients still showed occipital spikes in the EEG even after the P.C.R. had been abolished with treatment. The fact that these localised spikes were not abolished may have implications for the reduced effect of valproate on partial seizures if it is assumed that photosensitivity reflects a secondarily generalised epilepsy (Harding 1984).

Early reports in therapy resistant patients on polytherapy suggested that only 53% of patients with primary generalised tonic-clonic seizures experienced more than a 75% improvement (Simon and Penry 1975).

Later reports of monotherapy in patients with tonic-clonic seizures however, suggested that over 90% of patients can become seizure free (Dulac and Arthuis 1984), although in fact these authors misquote Covanis, Gupta and Jeavons (1982) who actually found that 80% of patients were controlled, 73% of these being on monotherapy. These latter authors conclude that Vpa is the "most effective drug for absence seizures and myoclonic epilepsy and very effective in primary tonic-clonic seizures..... If there is doubt as to whether tonic-clonic seizures are primary or secondary it is preferable

to use carbamazepine as the first drug".

Sodium valproate in the treatment of partial seizures

Early attempts to assess the use of sodium valproate in patients with partial seizures included open trials on subjects with severe epilepsy who had not responded to other AEDs. In most cases sodium valproate was added to concurrent medication and conflicting results were often produced.

The frequently cited review by Simon and Penry (1975) shows that of 10 studies including patients with "partial seizures with elementary symptomatology" only 46% of patients had a reduction in seizure frequency of greater than 75%. For patients with "partial seizures with complex symptomatology" the figure was 35%.

Subsequent studies by Harwood and Harvey (1976) and Haigh and Forsyth (1976) still produced conflicting results. The former authors found a 90% reduction of attacks in a third of patients with temporal lobe epilepsy and a similar reduction in just under a third with focal epilepsy. The latter authors found virtually no response in 14 patients with temporal lobe epilepsy or secondarily generalised tonic-clonic seizures who were mainly on valproate alone but in whom other AEDs had proved ineffective.

More stringently controlled experiments however, began

to place the value of valproate into perspective.

Turnbull, Rawlins, Weightman and Chadwick (1982) studied 88 patients over the age of 16 years with a history of 2 or more seizures in the last 3 years. Patients were randomised to either sodium valproate or phenytoin. Results showed that both drugs were equally as effective in patients with tonic-clonic seizures without obvious focal signs although the authors note that some of these patients may have had secondarily generalised seizures. Eighty three percent of patients on valproate became fit free as did 71% on phenytoin. Of the patients with partial seizures with or without secondary generalisation, 30% became fit free on valproate and 35% on phenytoin. It was thus demonstrated that valproate was almost equally as effective in patients with partial seizures as phenytoin.

Shakir (1980) produced similar evidence to suggest that monotherapy with valproate was equally as effective as monotherapy with phenytoin in patients with both partial seizures and generalised tonic-clonic seizures. Preliminary results in a total of 15 patients on valproate only, and 10 patients on carbamazepine only, suggested that these drugs were equally as effective without preference for the type of epilepsy.

Trials of monotherapy with sodium valproate in patients with partial seizures therefore began to show more

promising findings. Unfortunately, such studies are still few, most authors preferring to use carbamazepine as the drug of choice as suggested by Jeavons, Covanis and Gupta (1980), with valproate as an adjunct if carbamazepine is not effective alone.

Three recent studies have clarified findings still further. There was an obvious need to study newly diagnosed patients instead of those whose attacks had proven resistant to other AEDs. Goggin, Crowley and Callaghan (1983) compared serum levels in patients randomly allocated to valproate, phenytoin or carbamazepine. Results showed no statistically significant difference between the effectiveness of the 3 drugs when all seizure types were included. Insufficient information was available to assess responses to different seizures types. However, results did show that patients with partial seizures required a higher serum level of valproate than patients with generalised seizures (507umol/l compared to 398umol/l). Goggin et al. therefore propose two possible therapeutic ranges for valproate, this requires further investigation.

Secondly, Loiseau (1984) carried out an open crossover study of sodium valproate versus carbamazepine in previously untreated patients with partial epilepsy. After one year, 11 of 14 patients were seizure free on valproate and 8 out of 9 on carbamazepine. Loiseau therefore argues that in a more representative sample

valproate appears to be at least equally as effective as carbamazepine in patients with partial seizures.

Finally, Callaghan, Kenny, Crowley & Goggin (1985) randomly allocated 181 previously untreated patients with partial or generalised tonic-clonic seizures to sodium valproate, carbamazepine or phenytoin monotherapy. Results showed that "all three drugs can be prescribed as an anticonvulsant of first choice. Irrespective of the drug prescribed, partial seizures were less responsive to treatment".

Mechanisms of action

The mechanisms of action of valproate remain to a large extent uncertain. Several different mechanisms have been proposed and are well reviewed by Johnston (1984).

One of the earliest studies carried out, suggested that valproate actually increased brain levels of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) (Godin, Heiner, Mark and Mandel 1969). This was thought possibly to be due to the fact that valproate inhibits GABA metabolism by decreasing the levels of GABA-transaminase which breaks down GABA.

However, several objections to this hypothesis have since been raised. Firstly, valproate has been shown to

be only a weak inhibitor of GABA-transaminase requiring extremely high doses well above the therapeutic range, to produce in vivo inhibition. Secondly, valproate has an anticonvulsant effect on some seizures in lower doses than those required to increase brain GABA levels. Thirdly, protection from electric shock induced seizures has been found 2 minutes after administration of valproate whereas increased brain GABA levels are not seen for at least a further 20 minutes. Finally, no effect on GABA neurochemistry has been found when valproate has been used in therapeutic levels.

It would therefore seem that increases in GABA levels in the brain are an unlikely answer to the mechanism of action of valproate.

A second possibility which is reviewed by Johnston is the hypothesis that valproate may potentiate post-synaptic GABA responses. In vivo experiments have shown that iontophoresed valproate produces an increase in the response of cortical neurones to iontophoresed GABA. However, in most cases the valproate was dissolved in a solution with a high pH value and therefore some of the changes in spontaneous firing rates may have been due to changes in local pH.

Furthermore, experiments using valproate dissolved in neutral saline showed no effect on GABA responses using concentrations of valproate within the therapeutic range,

a good effect was only obtained at much higher concentrations.

The mechanisms of action of valproate have also been discussed by Morre, Keane, Vernieres, Simiand and Roncucci (1984). One of the possible mechanisms of action which they propose is the effect of valproate on potassium (K^+) at the cellular level. Non-mammalian studies have shown that certain cells in the hippocampus and cortex produce bursting activity during inter-ictal spikes. Excitability of these cells is increased if the outward flow of K^+ ions is restricted, or the inward flow of Na^+ and Ca^{2+} ions is increased. In fact it is the K^+ efflux which terminates the burst activity and it has been shown that valproate may increase or activate this efflux. Johnston (1984) however, has pointed out that the concentrations of valproate administered to the invertebrates was again 15 to 50 times greater than that given to patients.

Two other possible mechanisms of action are discussed by Gram (1981). It has been suggested that it is not the valproate itself which is active but one of its metabolites. However, it has been shown that none of the metabolites have anticonvulsant properties anywhere near as effective as valproate itself.

Valproate has also been found to decrease whole brain concentrations of aspartate which is an excitatory transmitter. It has not however been shown that

valproate actually decreases the synaptic release of aspartate and so this theory requires further testing.

Thus the mechanisms of action of valproate are still uncertain. Many of the studies mentioned, involved concentrations in higher doses than those found to produce a therapeutic effect in humans. As pointed out by Gram (1981) since valproate is effective in several different types of epilepsy it may have several mechanisms of action.

Pharmacokinetics

The pharmacokinetics of valproate are well reviewed by Woodbury (1982, Chapters 44, 45 and 48) and by Wilder and Bruni (1982).

The sodium salt of valproic acid is a white crystalline powder which is soluble in water. It belongs to the group of drugs known as carboxylic acids. In this form, the drug is almost totally absorbed into the body via the intestine, only 1.8% is excreted in the urine after a single oral dose. Its renal clearance being very small would indicate that a high proportion is re-absorbed.

The enteric coated tablet reaches peak concentration in the body 3 to 8 hours in normal subjects after fasting, ingested after a meal it takes longer. In

epileptic patients, peak concentrations are achieved in a shorter time ($\frac{1}{2}$ to 1 hour less) probably due to concurrent medication interactions. Serum levels are discussed in further detail in Chapter 5.

Similarly, the half-life of sodium valproate is slightly longer in normals (9.5 to 17.7 hours) compared with a mean half-life of 9 hours (6 to 12 hours) in epileptic patients, its clearance rate is also slightly greater in patients on other drugs. In patients a steady-state sodium valproate level would be expected after a minimum of approximately 2 days (5 half lives).

The therapeutic range of plasma levels has been found to be from 50ug/ml to 100ug/ml although some patients are only controlled at even higher levels. Some authors found a linear relationship between plasma level and dosage, although only in patients on monotherapy (these patients also achieve a higher plasma level on a lower dose). Other studies in patients on polytherapy have reported a curvilinear relationship between sodium valproate dose and plasma concentrations.

Only the non-protein bound drug is free to cross membranes and penetrate the brain. Sodium valproate is highly protein bound at low doses and becomes disproportionally less bound at higher doses. Protein binding becomes saturated at 50ug/ml - the

lowest therapeutic level - and so the ratio of free to total NaVpa begins to increase. Thus, the measurement of free drug levels is of paramount importance in plasma level monitoring.

Sodium valproate interactions with other drugs are well reviewed by Mattson (1982). Interactions with phenobarbitone have been noted causing serum phenobarbitone levels to rise leading to sedation. Conversely, phenytoin levels are found to drop when Vpa is added and although an interaction with carbamazepine is suspected it remains unclear. Jeavons and Clark (1974) have reported absence status in 5 patients on clonazepam, although other studies have shown that serum levels are not affected.

Side effects of sodium valproate

One of the earliest and most extensive studies of side effects of sodium valproate was carried out by Clark, Covanis, Gupta and Jeavons (1980). These authors studied 392 patients on dosages of sodium valproate between 20 and 26mg/kg. Sixty seven percent of patients experienced no unwanted effects.

One of the most frequent side effects was weight gain which occurred in 25% of females and 11% of males. In most cases, but not all, this was due to an increase

in appetite which may have been secondary to reported increased alertness. Harding, Pullan and Drasdo (1980) used a reaction time task as a measure of alertness in 33 photosensitive patients before and during treatment with sodium valproate and found that the mean reaction time was significantly shorter whilst on treatment. This was thought to be a direct CNS effect and was not related to the improvement in the background EEG.

Further side effects observed by Clark et al. (1980) were hair changes. In most cases this consisted of temporary thinning, in some there was hair curliness and in a few hair thinning followed by waviness on regrowth. Drowsiness occurred in only 5 of 240 patients on valproate alone and in 4 this was due to a large evening dose. This was resolved by taking medication earlier or by dividing the dosage. Drowsiness was more common in patients receiving valproate in combination with barbiturates or benzodiazepines. In 6% of patients platelet counts below 120 were observed but this was temporary and there were no clinical signs.

Clark et al. conclude that when given alone, sodium valproate is free from unwanted effects except for weight gain and is less likely to cause sedation than all other AEDs.

This latter conclusion is also supported by Trimble and Thompson (1984) who, having reviewed the literature on sodium valproate and cognitive function, conclude that sodium valproate "has less of an effect than some of the other commonly used anticonvulsants".

The most recent review of adverse effects has been carried out by Schmidt (1984). This author collated findings from 16 trials on a total of 1,140 patients. He notes that most side effects were mild and transient, responded to dosage reduction and occurred mostly early in therapy.

Side effects were more frequent in patients on polytherapy, the most frequent being drowsiness (14.4%) particularly in patients on phenobarbitone. Valproate is known to increase phenobarbitone plasma levels.

Nausea or gastrointestinal symptoms were observed in 6% of patients but it is noted that the enteric coated tablets have drastically reduced this incidence. Tremor was reported in 1.5% of patients on polytherapy and 1% on monotherapy. Schmidt notes that plasma levels varied from 34.9 to 154.3ug/ml in patients with tremor so this does not appear to be dose-related. Nor was hair loss which occurred in 4% of patients. Overall, Schmidt concludes that there was an increase in adverse reactions in patients with

plasma levels higher than 120ug/ml. Of the 300 patients in whom adverse effects were seen, only in 2% was therapy discontinued.

Recent reports of hepatotoxicity leading to death and also the teratogenicity of sodium valproate have been reviewed by Jeavons (1984). Sixty seven cases of fatal hepatotoxicity were analysed and revealed the following tendencies. Thirty nine patients showed evidence of mental retardation or other neurological, metabolic or genetic abnormalities. Excluding one patient of 68 years, the mean age was 8.2 ± 7.8 years. Excluding 2 patients the mean duration of therapy was 73 ± 63 days with symptoms appearing in 75% of patients by 12 weeks. Only 4 patients were receiving valproate alone and there were frequent reports of intractable epilepsy and several types of seizure in each patient. Presenting symptoms in most cases consisted of vomiting, drowsiness, malaise and abdominal pain. In many, seizure frequency increased, several had a fever and several were jaundiced.

Jeavons also reports 21 cases of reversible hepatotoxicity. Abnormal liver function tests in the form of only transient rises in SGOT and SGPT were seen in only 44% of cases suggesting clinical evaluation was more representative than laboratory tests.

The dosage of valproate involved did not appear to bear any direct relation to the fatal cases, doses ranging from 12 to 99mg/kg with 8 patients receiving less than 20mg/kg.

Jeavons concludes that severe ~~hep~~hepatic disease in these patients represents an idiosyncratic response "suggestive of metabolic aberration with the production of toxic metabolites rather than hypersensitivity".

Reports of teratogenicity associated with sodium valproate are obviously biased by the fact that only abnormal births are reported. Jeavons (1984) was able to gather data on the outcome of 344 pregnancies in women taking valproate in the first trimester. Sixty eight children born were malformed and in 28 cases the mother was receiving valproate alone. The most common malformation in babies of mothers receiving either monotherapy or polytherapy was neural tube defect. As the risk of spina bifida is estimated at 1%, Jeavons advocates pre-natal counselling. He also points out however, that the role played by anti-convulsants in birth malformations remains in doubt as the risk of abnormal births is also high in offspring of parents with epilepsy not on medication.

Nevertheless, ^{some} recent doubts have been expressed by several workers in the field with regard to administration of sodium valproate as the drug of choice in

female patients of child bearing potential with primary generalised epilepsy (Personal communication)

4.2 AN INVESTIGATION INTO THE EFFECT OF ONCE DAILY SODIUM VALPROATE COMPARED TO TWICE DAILY IN THE TREATMENT OF GENERALISED EPILEPSY.

Introduction

The therapeutic effects of valproate have been shown to be unpredictable in relation to its pharmacokinetic properties. This was demonstrated originally in animal studies. Lockard and Levy (1976) showed that seizures were reduced in 12 Rhesus monkeys for up to 2 weeks after valproic acid had been withdrawn even though after the first post drug day none of the drug was detectable in blood plasma. This finding was subsequently demonstrated in humans, Harding, Herrick and Jeavons (1978) showed that the anticonvulsant properties of sodium valproate continued for up to 3 months after withdrawal of the drug in patients with photosensitive epilepsy.

Van Duijn, Meijer and Segers (1977) showed that more

valproic acid entered the brain of cats if it was administered in a large concentrated dose rather than in smaller doses with the continuation of constant blood levels. In a similar vein, Walter, Boardmans, Harry, Howe, Lead and Smith (1978) showed that a large single dose of valproate protected mice from seizures more efficiently than multiple doses.

These findings have inspired other authors to manipulate dosage regimes in human patients. With a half life of between 6 and 12 hours (in human epileptic patients) it had hitherto been assumed that the drug should be administered in 3 or 4 daily doses. This protocol would ensure that plasma concentrations did not fluctuate excessively due to the drug's limited half-life.

Cenraud, Guyot, Levy, Brachet-Lierman, Morselli and Louiseau (1981) examined the difference between plasma levels in 6 patients on twice-daily enteric coated sodium valproate and 6 patients on thrice-daily sodium valproate using hourly plasma sampling. They found firstly, that group mean fluctuations were less with 3 daily doses than with 2, secondly intra-individual fluctuations were less in 3 daily doses, but thirdly inter-individual fluctuations persisted.

Rowan, Binnie, de Beer-Pawlikowski, Goedhart, Guther, van der Geest, Meinardi and Meijer (1979) showed in 3

patients, that the fluctuations in serum levels of sodium valproate made no difference to its therapeutic effect. In fact, 3 out of 4 patients showed better control of seizure discharges on twice-daily doses rather than four daily doses.

The following groups of co-workers have used twice daily sodium valproate since 1974 and once daily since 1978. Covanis and Jeavons (1980) describe 35 patients all controlled on a once daily regime. Twenty one of these patients had previously failed to respond to other anti-epileptic drugs, in 14 valproate was the initial drug therapy, 7 patients having been started on once daily originally.

Seven patients were investigated for serum levels and these were found to be similar both for once daily and twice daily regimes.

Covanis and Gupta (1980) describe 31 patients in whom seizures were controlled on once daily valproate. Seventeen patients had been changed from twice daily to once daily and in 9 who had previously had abnormal EEGs, the EEG became normal. Fourteen other patients had been started on a once daily regime from the beginning of therapy.

This work culminated in the 1981 work (Covanis, Jeavons and Gupta) in which 66 patients free from seizures on once daily NaVpa were discussed. Thirty-six patients

were assessed on clinical grounds, 20 of these who had been changed from twice daily to once daily remained seizure free, 14 were seizure free on once daily valproate from the beginning of therapy and in 2 with infrequent seizures the EEG became normal.

Thirty patients were assessed on their response to intermittent photic stimulation in the EEG. Fifteen of these were changes from twice to once daily, in 7 of these the EEG remained normal and in 6, previously seen abnormalities disappeared. Only 2 patients showed no improvement. The remaining 15 patients had been started on once daily and showed no abnormalities.

Overall, 64 out of the 66 patients were assessed on their EEGs both before and after treatment. A total of 41 EEGs were normal on a single dose of valproate (11 after changing from twice to once daily), although in view of the possible delayed effect of valproate (Stefan et al. 1984 and Martinovic 1983) it is possible that some of these findings were due to an increased time factor.

In 35 patients studied, there was no significant difference in serum levels whilst taking a once or a twice daily dosage despite the fact that on OD, serum was measured 12 to 14 hours after ingestion and on BD, 3 to 4 hours after ingestion.

The studies mentioned so far assess the effect of valproate mainly on the clinical response or the basic EEG. Other studies have looked at the effect of valproate on the long-term EEG. Until recently, these studies have required the use of telemetry.

One of the earliest studies carried out using telemetry was that of Villareal, Wilder, Willmore, Bauman, Hammond and Bruni (1978) using 6 hour cable telemetry. These authors gave valproic acid in three daily doses to 25 patients. Twenty three patients were receiving co-medication and 23 were judged to be refractory.

Four patients had absences only. Other patients had tonic-clonic seizures, myoclonic attacks and partial seizures as well as absences. Results showed a reduction in the number of spike and wave discharges in the 6 hour telemetered EEG whilst on therapy compared to a placebo period in 19 patients. A reduction in the total duration of discharges was found in 21 patients.

No correlation was found between the percentage reduction of discharges and the serum level of valproic acid after 10 weeks of therapy, although improved patients had plasma levels of greater than 50 to 60ug/ml.

Surprisingly, no correlation was found between the

reduction in discharges and the clinical response except in 13 patients. They note that some patients who showed a poor EEG response showed a good clinical response and 2 patients even showed a good clinical response and poor EEG response. Several factors may explain these findings, only two of which these authors recount. Firstly, patients may not accurately report their seizures. Unfortunately, the authors do not enlarge on this. This may be due to the fact that some patients also had partial seizures which can be difficult to distinguish from absence seizures and also that discharges of less than 3 seconds duration may not be accompanied by clinical changes.

Secondly, the authors note that the EEG results may be affected by environmental and physiological changes such as menstruation and stress, however one would have assumed that the clinical response would be equally as affected. Many of the findings are undoubtedly due to the fact that the clinical response was assessed over the duration of therapy whereas the EEG response was based on one 6 hour telemetered EEG. This 6 hour period may be inadequate due to the length of sampling time (this appears also to have included periods of sleep), and also because the patient was in an alien environment in a laboratory which may influence the frequency of occurrence of discharges. Such findings highlight the need for ambulatory monitoring in the home to be used in such studies.

Rowan, Overweg and Meijer (1981) also used telemetry to study monodose valproic acid. Three patients on sodium valproate twice daily, and one patient on 4 daily doses (3 were on co-medication) were changed to once daily (O.D.) valproic acid using the appropriate correction factor. There was observed clinical improvement in 3 and in one no change. Unfortunately, the EEG itself is not discussed and it is regrettable that in this study the change from sodium valproate to valproic acid confounded results.

Work which is most relevant to the present study has been carried out by Stefan, Burr, Fichsel, Froscher and Penin (1984). These authors assessed once daily administration of sodium valproate in 18 previously untreated patients with absences or tonic-clonic seizures. Ambulatory EEG monitoring was performed prior to treatment then patients were started on a dosage of 10-12mg/kg sodium valproate given at 8.00pm. If the ambulatory EEG still showed abnormality the dosage was increased and the recording repeated after 1-2 weeks, after 3-12 weeks and finally after more than 4 months.

Results showed that the mean reduction in spike and wave activity for all patients on the final recording was 90%. The mean body weight to dosage ratio was 15.6mg/kg ranging from 10mg/kg to 25mg/kg.

Individual response patterns included a) A continuation of the reduction in discharges even after valproate had reached a steady state. b). A large decrease in discharges after a certain therapeutic range had been reached and then smaller decreases which were brought about by small increases in valproate. c). A delayed effect of treatment seen only after 2 months although it is debatable in the patient shown, whether the delay occurred due to the time factor or the change in dosage. d). Some patients showed a suppression of regular discharges and little initial change in brief irregular discharges.

Other findings were that the mean duration of discharges decreased more slowly than the total duration, and in some patients a temporary rise in the mean was seen between the second and third recordings. In some patients longer discharges were abolished but very brief ones were not.

The clinical response was also assessed. In 10 patients no absences were reported between the second recording and the last recording. They note that "the tendencies of seizure and discharges were essentially similar".

The authors found that in the 4 patients who showed least response, attacks had first appeared several years earlier or there were also tonic-clonic seizures.

This is surprising as they then state that in the 10 to 14 year old group the dosage was 16.4mg/kg and in the 16 to 48 year old group the dosage was lower, (14.4mg/kg).

They surmise that the effect of valproate is delayed but it is possible that some of the findings may be due to natural day to day variations.

Few side effects were reported and this was assumed to be due to the low dosages employed.

Thus, ambulatory monitoring enabled Stefan et al. (1984) to monitor patients EEGs at home, in real life circumstances without the possible problems encountered by Villareal et al. (1978) who used telemetered periods in the laboratory. Ambulatory monitoring also helped Stefan et al. to fine tune the dosage regime so that the minimal amount of drug was given concomitant with EEG control and the incidence of side effects was reduced.

One of the problems associated with monitoring the EEG in such patients is in deciding when adequate control has been achieved. There is now evidence to suggest that even brief discharges may have an adverse effect on performance.

Penry (1973) using telemetry, showed that spike and wave bursts of less than 3 seconds were unidentified during intensive observation 'unless the patient was speaking, writing or engaged in fine movements of the upper extremities'. In a review of the literature, he noted that visual and auditory reaction times were not impaired in paroxysms lasting for less than 2 seconds. During 3 to 6 second discharges however, impairment was present. Other studies using more stringent experimental control showed that reaction times were impaired in paroxysms lasting 0.5 to 1.5 seconds, although there was no increase in errors of omission. Pursuit rotor performance was impaired after 3 seconds of discharges, the errors beginning well after the onset of spike and wave activity.

Aarts, Binnie, Smit and Wilkins (1982) have shown that in 13 out of 36 patients there was transitory cognitive impairment on a topographical test (reproducing random sequences of coloured rectangles) during short discharges without any overt signs. Eight out of 23 patients also showed impairment on a similar verbal task.

Thus it is important to abolish all discharges if possible, particularly in children in whom discharges may impair learning. In adults wishing to obtain driving licences whose overt attacks are controlled, this may

also be important, although not required by law.

The following study employs ambulatory monitoring in a similar way to Stefan et al. (1984) but it is also aimed at assessing the efficacy of once versus twice daily administration of sodium valproate in a more controlled study than those previously reported.

Method

Patients

Twenty untreated patients with spontaneous generalised spike and wave discharges in their EEG were randomly allocated to once or twice daily sodium valproate enteric coated. The mean age for the once daily (OD) group was 10.8 years and for the twice daily (BD) it was 9.2 years. The mean weight for the OD group was 42.5kg and for the BD group 31.2kg. There were 5 males and 5 females in each group. Details of each patient are given in Tables 4.1 and 4.2.

All patients but one, (M.Na) were newly diagnosed. None, except for this patient, had previously been treated with anticonvulsants.

Spontaneous discharges of spike and wave activity were present in the basic EEG of all patients except for M.Na whose discharges only became apparent on ambulatory recording. In most patients the spike and wave activity

TABLE 4.1

DETAILS OF PATIENTS ALLOCATED TO
ONCE DAILY SODIUM VALPROATE

	Age (years)	Sex	Weight (kg) at start of trial
K.S	10	F	35
E.C	10	F	35.4
M.M	11	M	36.7
M.N	6	M	23.6
L.B	10	M	34.5
S.J	7	M	30
J.G	8	F	22.7
J.T	12	F	42
MNa	20	M	92
S.P	14	F	73.5
Mean	10.8		42.5
S.D	4		22.4

TABLE 4.2

DETAILS OF PATIENTS ALLOCATED TO
TWICE DAILY SODIUM VALPROATE

	Age (years)	Sex	Weight (kg) at start of trial
S.B.	8	F	35.4
L.E	8	F	20.4
J.P	10	M	29.9
J.O	12	M	44.5
R.M	9	M	32
P.J	7	M	24
JGa	8	F	24
D.B	10	M	29
T.F	9	F	24.5
C.M	11	F	48.5
Mean	9.2		31.2
S.D	1.6		9.2

was mainly at 3cps. One patient in the OD group and one in the BD group showed faster components at 5cps. Five patients in each group showed mild clonic components consisting of eyelid flutter and 2 in each group showed mild tonic components. One patient (K.S) showed only staring in association with attacks. Two patients (J.T and J.Ga) had shown no clinical absence attacks but J.T experienced a seizure whilst watching T.V. and a subsequent EEG recording revealed spontaneous discharges and also photosensitivity. J.Ga, was the identical twin of J.G, in whom attacks had been observed.

Five patients in all were photosensitive, and one in each group had experienced attacks associated with flashing light. In these patients the aim was first to abolish spontaneous discharges and then to assess the photosensitive range using the method of Jeavons and Harding (1975). Details of the EEG and clinical attacks are given in Tables 4.3 and 4.4.

Apparatus

All patients were recorded on a 3 channel ambulatory EEG recorder with a time/event channel. The montage used can be seen in Figure 3.2. This montage has been found to adequately monitor generalised discharges whilst reducing the amount of muscle artefact from the jaw and also recording a good alpha rhythm. Recordings were replayed using the P.M.D.12 visual playback unit.

TABLE 4.3

EEG AND CLINICAL DETAILS OF PATIENTS

ALLOCATED TO AN OD REGIME

	<u>Spike & Wave</u>	<u>Absences (clinical)</u>	<u>Other</u>
K.S	3-4 c.p.s.	staring only	+ tonic-clonic
E.C	3 c.p.s.	automatisms	+ P.S
M.M	2-4 c.p.s. initial polyspikes	automatisms and mild clonic	+ P.S
M.N	3 c.p.s.	automatisms mild tonic	
L.B	3 c.p.s.	mild clonic, mild tonic	+ tonic-clonic + R parieto-occipital sharp waves
S.J	3 c.p.s.	automatisms and mild clonic	
J.G	3-4 c.p.s. irregular	automatisms	+ L rolandic sharps
J.T	5 c.p.s.	nil	+ P.S.E with myoclonia + R rolandic sharps
M.Na	3-4 c.p.s.	mild clonic	
S.P	3-5 c.p.s.	staring only	
	P.S = photosensitivity	P.S.E. = photosensitive epilepsy	
	L = Left	R = Right	

TABLE 4.4

EEG AND CLINICAL DETAILS OF PATIENTSALLOTTED TO A BD REGIME

	<u>Spike & Wave</u>	<u>Absences (clinical)</u>	<u>Other</u>
S.B	3 c.p.s.	automatisms	
L.E	3 c.p.s.	automatisms and mild clonic	
J.P	3 c.p.s. initial polyspikes	mild clonic, mild tonic	
J.O	2.5-3 c.p.s.	mild clonic	
R.M	3-5 c.p.s. irregular	mild clonic	+ P.S
P.J	3-4 c.p.s.	automatisms, mild tonic	
J.Ga	3-4 c.p.s. irregular	nil	+ L rolandic sharps
D.B	3 c.p.s. initial polyspikes	automatisms, mild clonic	
T.F	2.5 c.p.s. irregular, polyspiking	myoclonic	severe P.S.E. with myoclonia
C.M	3 c.p.s.	automatisms	P.S.E
	P.S = photosensitivity	P.S.E. = photosensitivity	
	L = Left	R = Right	

Procedure

The study was approved by the Ethical Committees of the Birmingham Children's Hospital and also that of the University of Aston.

Details of the proposed investigation were sent to all local consultants. The indications for inclusion in the study was that the patient should have spontaneous generalised spike and wave discharges and he or she should not be receiving any other anticonvulsant medication. Male and female patients over the age of 5 years were included.

Referring consultants were asked to telephone the clinic as soon as possible after seeing the patient. The patients were then given an ambulatory EEG appointment, usually in the same week, so that medication could be started as soon as possible.

On arrival at the clinic, patients were given a full explanation of the trial, they were given a list of the possible side effects of sodium valproate and they or their parents were asked to sign a consent form. A basic 16 channel EEG was then performed followed by a baseline 24 hour recording using the procedure described in Section 3.1. Many patients were reluctant to go to school wearing the apparatus so it was arranged that the equipment should be applied on a Friday evening and removed by the parents on a Saturday evening. This prevented children missing lessons unnecessarily. Patients and parents were reminded to press the event button if an

attack was noticed. They were also asked to fill in a diary sheet of daily activities and to note the time of any attacks.

After one baseline recording without medication, patients were randomly assigned to either a once or a twice daily regime. After each increase in dosage patients underwent a further 24 hour recording. The dosage schedules can be seen in Table 4.5. The starting dose depended on the weight and the clinical history.

In addition three patients underwent two consecutive baseline recording days in order to assess intra-subject variability.

Therapy commenced on the day after the baseline recording. Patients assigned to an OD regime were asked to take their medication at 8.00pm or as close to this as possible and those on BD at 8.00am and 8.00pm.

A minimum of 7 days was allowed to elapse between each increase in dosage and the next 24 hour recording. If spike and wave activity was present to a sufficient extent to warrant an increase in medication, parents were informed by telephone.

Patients were crossed over to the alternative regime at the same dosage if control was not achieved at 30mg/kg or if control was almost present and there was insufficient abnormality to justify increasing the dosage.

TABLE 4.5

DOSAGE REGIME (mg)

<u>O.D</u>	<u>B.D</u>	<u>Patients S.P and M.Na) (O.D)</u>
* 200 nocte	200 nocte	500 nocte
400 nocte	200 nocte 200 nocte	1000 nocte
600 nocte	200 nocte 400 nocte	1500 nocte
800 nocte	400 nocte 400 nocte	2000 nocte
1000 nocte	500 nocte 500 nocte	2500 nocte
		3000 nocte
		3500 nocte

* depending on weight of patient and clinical history

Patients were asked how they felt at each visit to the clinic so that any side effects could be documented. Once adequate control had been achieved a further 24 hour recording was performed in order to ensure that control was reliable.

Reports were sent to the referring consultant after each investigation. Routine haematology, liver function tests, urinalysis and plasma drug levels were only carried out at the discretion of the referring clinician.

Analysis

Each record was replayed at 20 or 60 times real time. The time and duration of each discharge during waking was noted on the patient's diary sheet. In all patients but 2, all discharges were counted. Patient S.P. showed very frequent brief discharges which were only possible to assess by number and not duration. Patient T.F. also showed very frequent brief discharges which were impossible to count as well as discharges of longer duration. In this patient, at first, only discharges of longer than 3 seconds were counted but later, discharges of longer than 1 second were counted.

Spike and wave activity during sleep was not assessed for this study.

RESULTS

Baseline recordings

There was a great deal of inter-subject variation in the total amount of spike and wave activity in 24 hours and also its mean duration. Ten subjects showed a total duration of over 500 seconds. Eight subjects showed between 100 and 500 seconds and 2 showed less than 100 seconds (Table 4.6).

There was also much variation in the mean duration of discharges. In 8 patients the mean duration was greater than 10 seconds, in 7 it was between 3 and 10 seconds and in 5 it was less than 3 seconds (Table 4.7). The overall mean was 9.7 ± 8.1 seconds. In the 3 subjects (J.O., J.Ga and L.B) who underwent two baseline recordings, results are shown in Table 4.8. For purposes of later analysis the first days recording was used as this showed the most abnormality in 2 out of the 3 patients.

Results showed considerable intra-subject variation particularly in subject J.Ga. Of the 3 measures, the mean duration of discharges would appear to be by far the most stable.

Relationship between the number of discharges and the mean duration.

In order to assess whether subjects with longer discharges

TABLE 4.6

TOTAL DURATION OF SPIKE & WAVE ACTIVITY
DURING BASELINE RECORDINGS

	Number of patients		
	<u>O.D</u>	<u>B.D</u>	<u>Total</u>
Over 500 secs.	5	5	10
100 to 500 secs.	4	4	8
less than 100 secs.	1	1	2

TABLE 4.7

MEAN DURATION OF SPIKE & WAVE ACTIVITY
DURING BASELINE RECORDINGS

	Number of patients		
	<u>O.D</u>	<u>B.D</u>	<u>Total</u>
less than 3 secs.	2	3	5
3 to 10 secs.	3	4	7
Over 10 secs.	5	3	8

TABLE 4.8

DAILY VARIATION IN DISCHARGES IN 3 SUBJECTS WHO
UNDERWENT TWO CONSECUTIVE BASELINE RECORDINGS

J.O

	Day 1	Day 2	% difference from day 1
Number	46	36	21.7
Mean duration	10.7	10.7	0
Total duration	494	385	22.1

L.B

	Day 1	Day 2	% difference from day 1
Number	114	169	48.2
Mean duration	3.3	3.1	6.1
Total duration	373.5	520.5	39.4

J.Ga

	Day 1	Day 2	% difference from day 1
Number	29	3	89.6
Mean duration	2.6	1.5	42.3
Total duration	75	6	92

showed fewer episodes or vice-versa, a Spearman's ranked correlation coefficient was carried out between the number of discharges and the mean duration of discharges of all subjects in the baseline condition (Table 4.9). Results showed a significant negative correlation of -0.5 at the 0.03 level. Results are plotted in Figure 4.1a. As there was little visual evidence in this scattergram that results were significant, the two highest scores were excluded so that remaining points could be expanded (Figure 4.1b). From this plot it can be seen that there is a tendency for patients with discharges of a longer mean duration to have fewer discharges whereas those with briefer mean durations showed more discharges.

Details of treatment in individual patients

The raw data for individual subjects is given in Appendix 8. The course of treatment in each patient is plotted in Figures 4.2 to 4.6. These graphs show the total and the mean duration of spike and wave in seconds at the various dosages and regimes.

In 3 subjects, sodium valproate was eventually withdrawn. These patients are included in Figure 4.2. The teacher noted that J.Ga constantly appeared drowsy in class, so she was withdrawn.

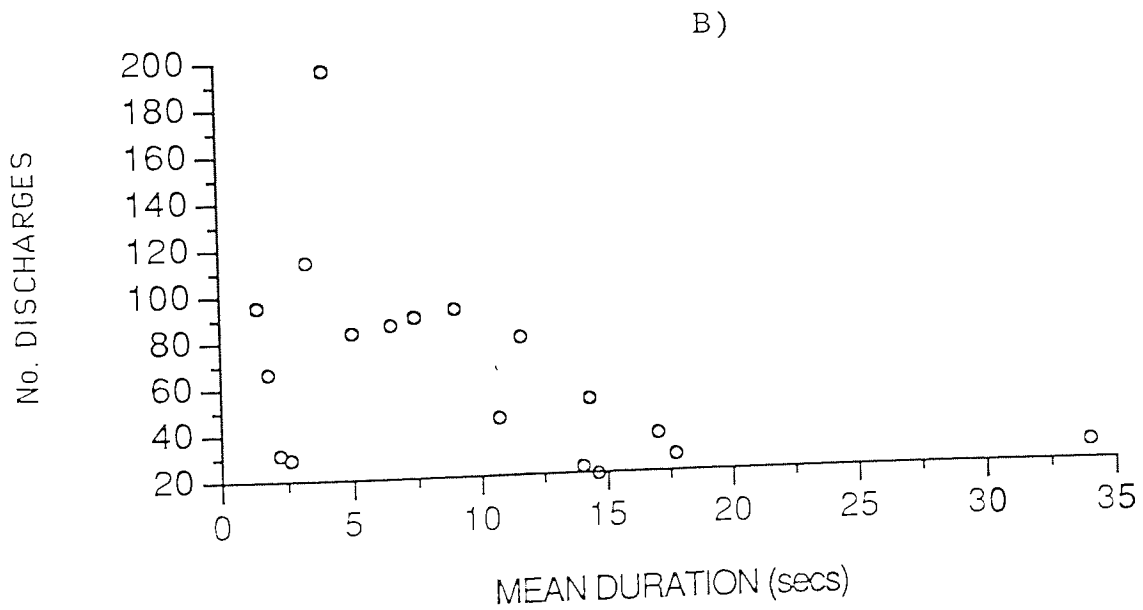
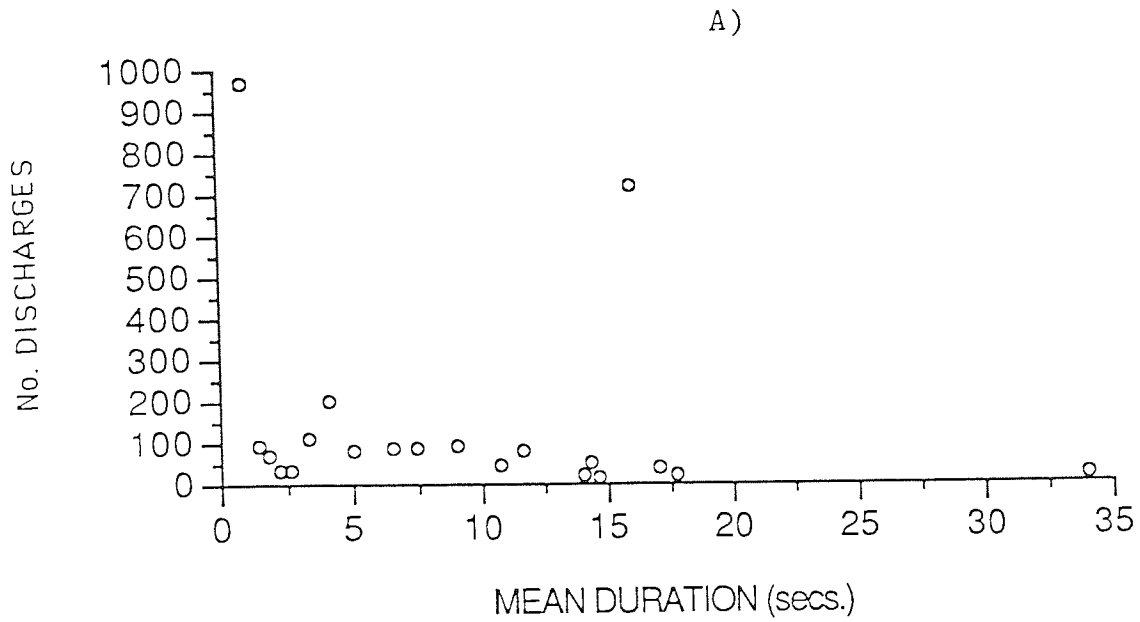


FIGURE 4.1

SCATTERGRAM SHOWING THE RELATIONSHIP BETWEEN THE MEAN DURATION OF DISCHARGES AND THE NUMBER OF DISCHARGES IN BASELINE RECORDINGS A) INCLUDING TWO VERY HIGH SCORERS AND B) EXCLUDING THE TWO HIGH SCORERS.

TABLE 4.9

NUMBER OF DISCHARGES IN BASELINE RECORDINGS COMPARED
TO MEAN DURATION OF DISCHARGES

<u>Patient</u>	<u>Number</u>	<u>Mean</u>	<u>S.D.</u>
KS	93	9	2.7
E.C	90	7.4	3.3
M.M	23	14	4
M.N	27	17.7	2.5
L.B	114	3.3	0.88
J.G	31	2.2	0.7
J.T	67	1.8	1.2
S.P	971	(approx 1sec.)	-
MNa	197	4.1	1.26
S.J	28	34	33.74
S.B	37	17	5
L.E	80	11.6	3.9
J.P	52	14.3	3.5
R.M	95	1.4	0.5
J.Ga	29	2.6	0.8
D.B	83	5	1.3
T.F	87	6.5	2. (NB those over 3sec.)
C.M	46	16	6
P.J	20	14.6	7.4
J.O	46	10.7	3

Spearman's correlation coefficient = -0.49

Significant at 0.03 level

Psychological testing and the teacher's assessment suggested no difference in performance whilst on or off medication despite a reduction in the number of discharges. As this child had not shown clinical attacks (although her twin sister had), further anticonvulsant treatment was not indicated. Control of discharges had been achieved in this patient at 600mg b.d. In order to bring her into line with her sister however, which made it easier for the mother, she was changed to an OD regime which also maintained control of discharges until medication was withdrawn.

Subject J.G. (the twin of J.Ga) showed an erratic response to treatment. The amount of abnormality varied from nil discharges whilst on 400mg OD to 118 seconds on 600mg OD despite good compliance. As the alteration in discharge rate could not be attributed to medication she was withdrawn from treatment. Neither twin has shown any clinical attacks since being withdrawn. An additional complication has now occurred in that recent basic EEGs revealed that both children have become photosensitive.

Subject L.E found it difficult to swallow tablets and was given Epilim syrup. On a BD dosage of 39mg/kg discharges had only reduced by half with a total of 298 seconds remaining. This dose cannot be given once daily as syrup, as 40mg/kg is the top dose for monotherapy, she had failed to respond. Ethosuximide subsequently abolished all attacks.

In patient C.M there was a sudden abolition of discharges at 600mg B.D which on repeat proved unreliable. Finally, on a dosage of 1000mg B.D and with 42 seconds of spike and wave remaining she repeatedly failed to attend appointments and was lost to follow-up.

This left 7 patients in the BD group and 9 in the OD group.

Of the 9 patients in the OD group (included in Figures 4.3 to 4.5) three were changed to BD. One (M.Na), was changed to a higher BD dosage at 2,500mg as there were considerable discharges remaining and the consultant was afraid that a dose of 3000mg given all at once, might cause sedation. On 3500mg BD only 11.5 seconds of spike and wave remained. He was still however, reporting occasional attacks on other days. The patient's prime concern was the acquiring of a driving licence and so the consultant agreed to try him on an OD regime. This resulted in an increase in the total duration of discharges to 58.5 seconds. He was therefore returned to the same divided dosage.

Subject S.J was changed independently by his parents to a lower BD dosage and improved. They then altered his regime to the same OD dosage which abolished all discharges.

The third patient whose regime was changed (K.S) experienced

a tonic-clonic seizure on 800mg OD but showed no spontaneous discharges the following day. In view of the tonic-clonic seizure the dosage was increased to 1000mg OD. Two consecutive recordings were then performed as it seemed likely that all discharges would disappear, however, on the second day there were no discharges and on the first day there was a total duration of 19 seconds. Instead of increasing the dosage, the regime was changed, which resulted in 2 consecutive recordings free from discharges.

In the remaining subjects receiving an OD regime, the course of treatment was uncomplicated except for subject S.P who showed a high serum level (174mg/l) at 2000mg ODs. Her dosage was therefore decreased to 1500mg OD which resulted in only very slight increase in discharges and a serum level of 72mg/l. It was interesting that this patient showed a 77% increase in discharges whilst she was menstrual despite the dosage remaining constant.

Of the 7 patients remaining in the BD group (Figures 4.5 and 4.6) three were changed over to an OD regime. Subject J.P was changed from 800mg BD to 800mg OD and all discharges were abolished although the resulting improvement was only by 5 seconds.

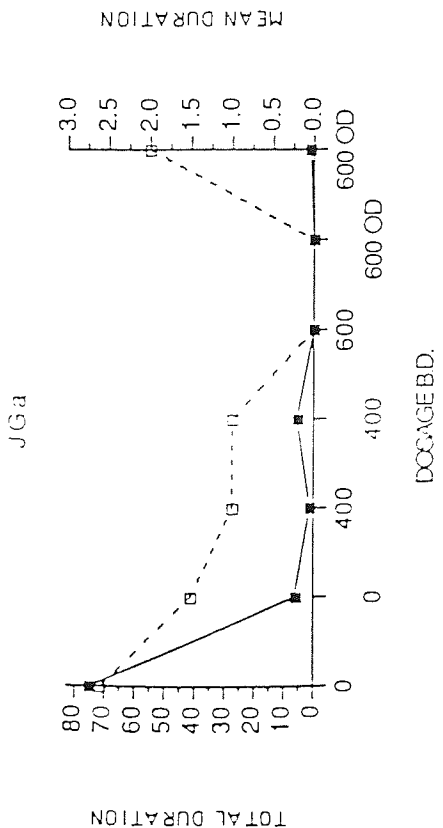
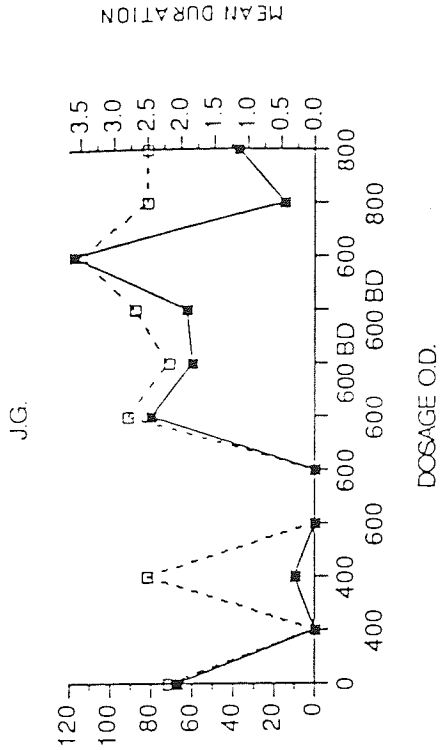
Subject P.J was changed by the parents from 400mg BD to 200mg OD and improved. This patient was the brother of the child in the OD group whose parents had adjusted medication themselves. There was also a change in

family circumstances at the time of total reduction of discharges.

The third subject (T.F) was changed from 600mg BD to 600mg OD (25mg/kg) without improvement. An increase in dosage to 800mg OD showed a slight increase in the number of discharges of greater than 1 second duration but she remained at this level as her photosensitivity was reduced.

In the 4 remaining patients on BD the course of treatment was uncomplicated.

Figures 4.2 to 4.6 show that in 11 subjects there was a sudden fall in the duration of discharges after the first or second dosage increment. In fact this appeared to occur on average at around 50% of the final dosage required to achieve control (range 14 to 80%). Three further patterns also emerged. In 7 of the subjects shown in Figures 4.3 and 4.5 there was an initial increase in the mean duration of discharges whilst the total duration decreased. In a further 5 subjects (J.T, J.O, T.F. J.Ga and C.M) the mean duration fell more slowly than the total duration and in remaining subjects it followed a similar pattern. No obvious differences on any other parameter could be found to distinguish these 3 groups.



■ TOTAL DURATION
□ MEAN DURATION

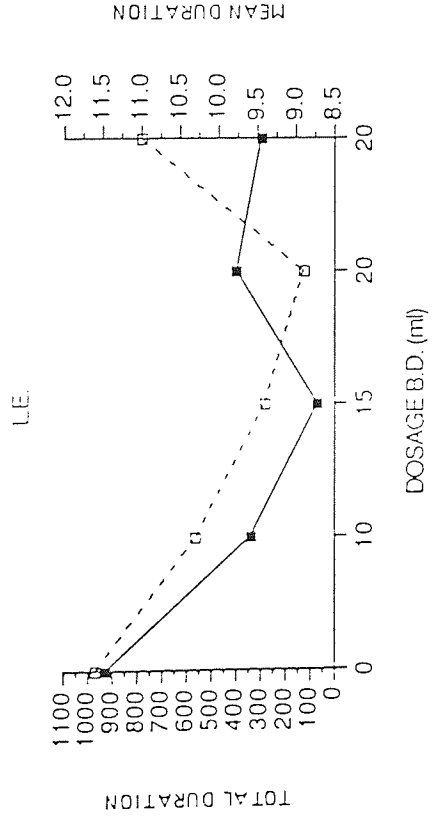
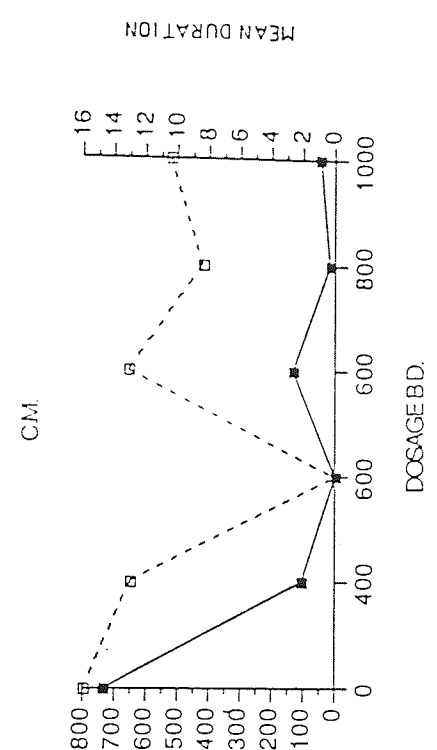
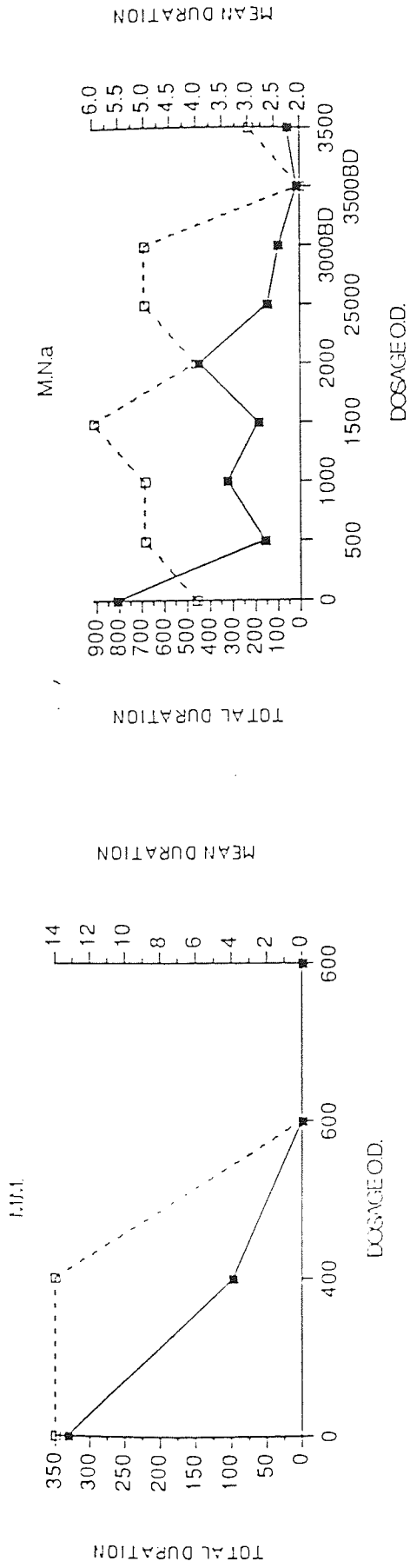


FIGURE 4.2
RESPONSE TO TREATMENT OF 3 SUBJECTS IN WHOM VALPROATE WAS
WITHDRAWN AND ONE SUBJECT LOST TO FOLLOW-UP.



■ TOTAL DURATION
□ MEAN DURATION

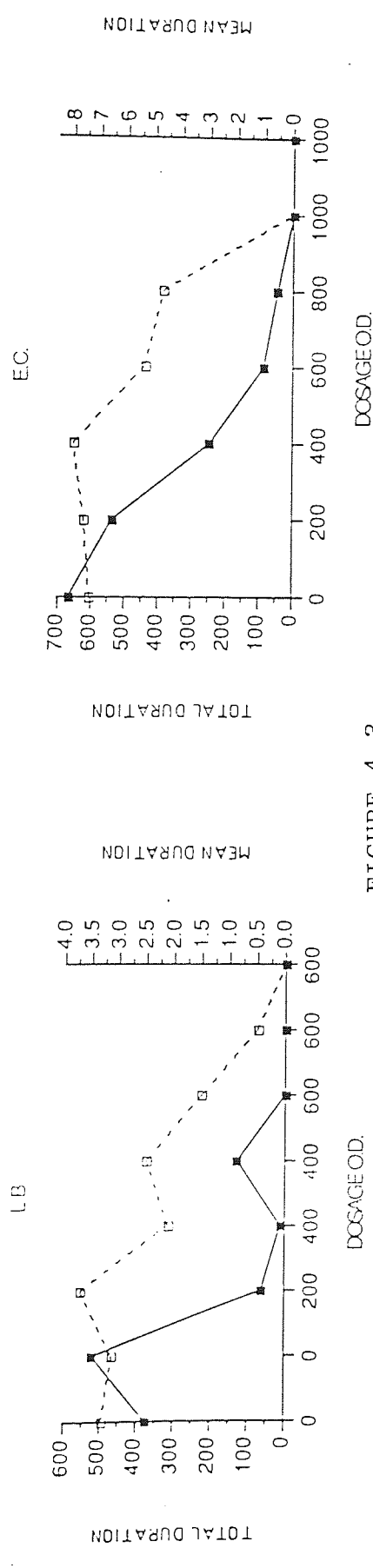
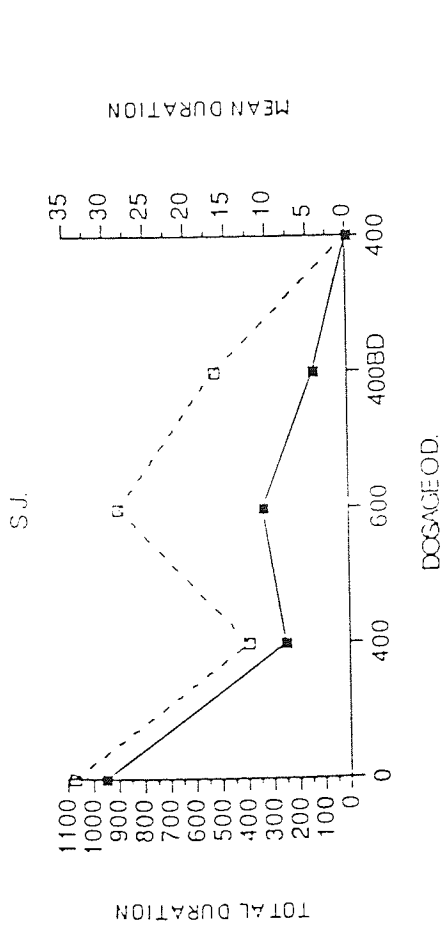
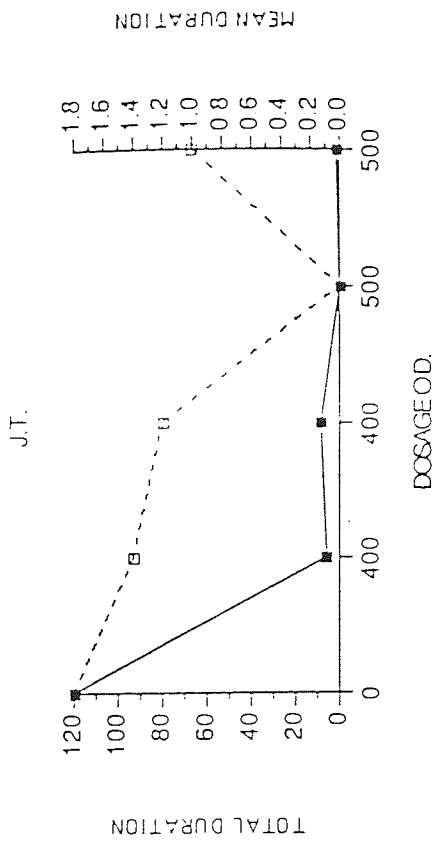


FIGURE 4.3
RESPONSE TO TREATMENT OF 4 SUBJECTS ON OD WHOSE MEAN DISCHARGE DURATION INITIALLY INCREASED.



■ TOTAL DURATION
□ MEAN DURATION

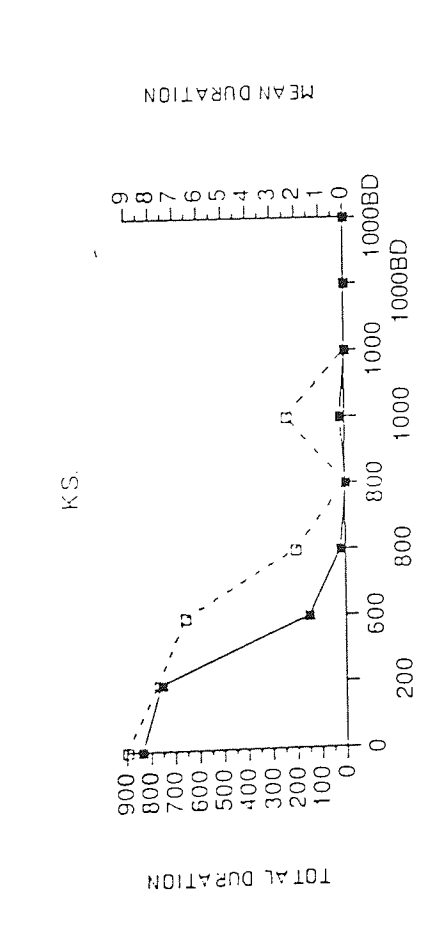
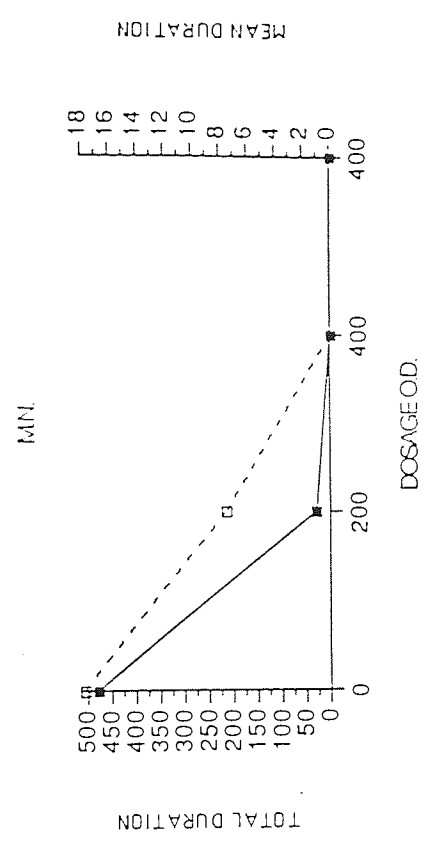
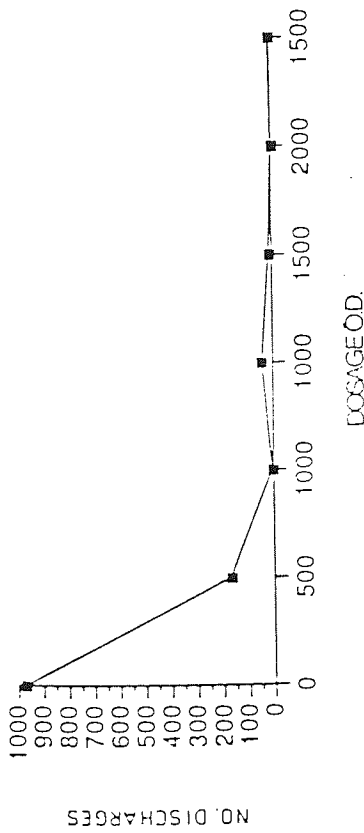
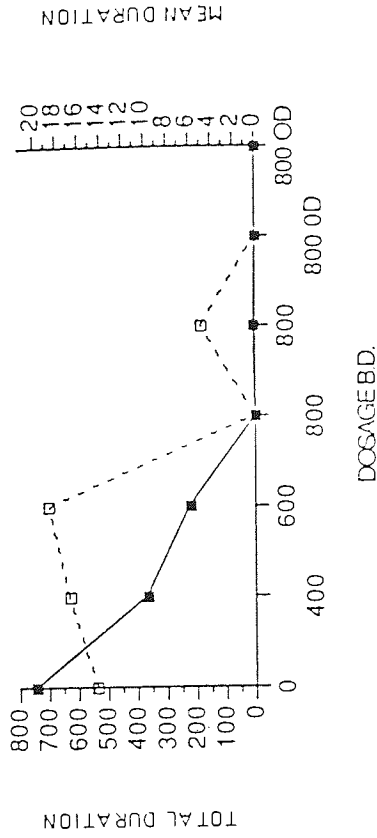


FIGURE 4.4
RESPONSE TO TREATMENT OF 4 SUBJECTS ON OD WHOSE MEAN
AND TOTAL DISCHARGE DURATION DECREASED.

S.P.



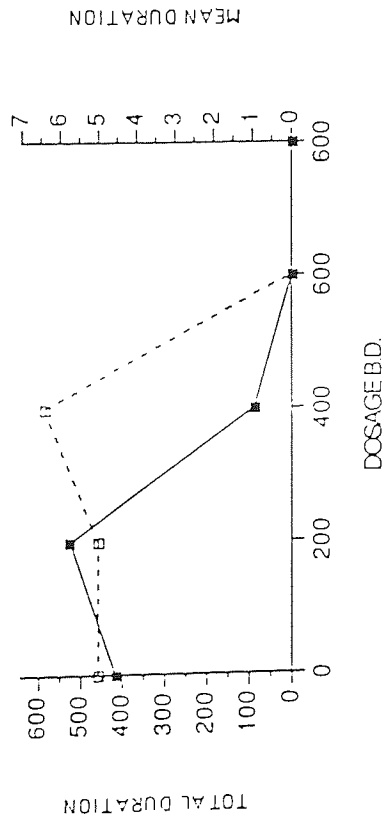
J.P.



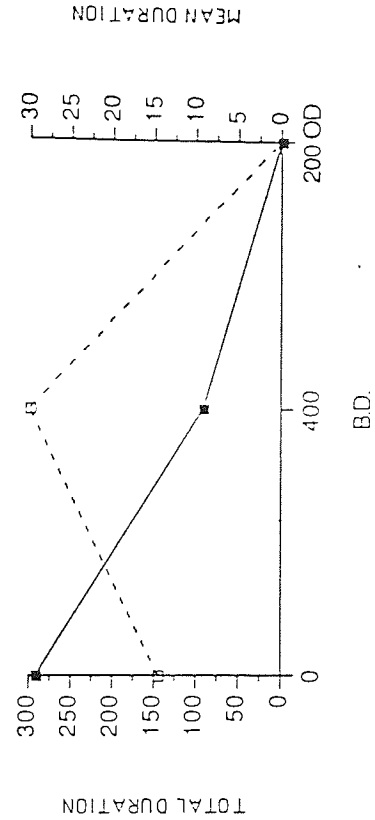
■ TOTAL DURATION

□ MEAN DURATION

D.B.



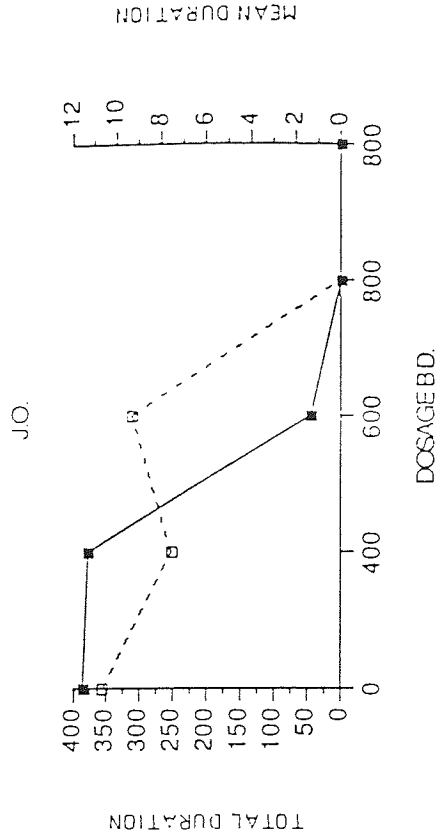
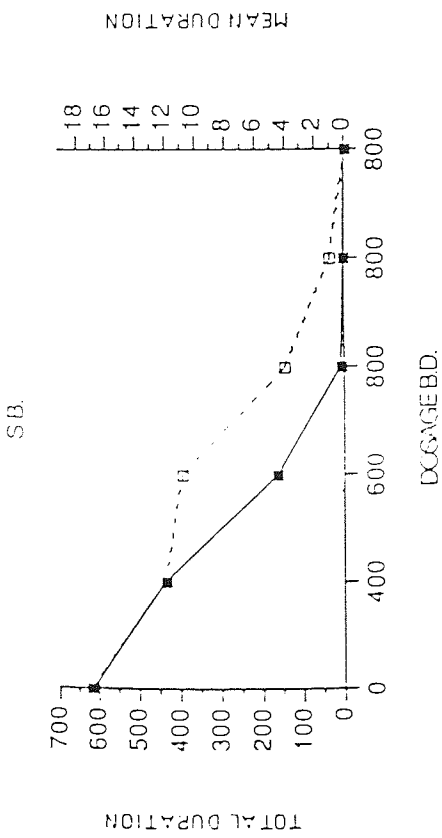
P.J.



DOSAGE B.D.

FIGURE 4.5

RESPONSE TO TREATMENT OF PATIENT S.P. (NUMBER OF DISCHARGES ONLY) AND 3 SUBJECTS ON BD WHOSE MEAN VALUES INITIALLY INCREASED.



■ TOTAL DURATION

□ MEAN DURATION

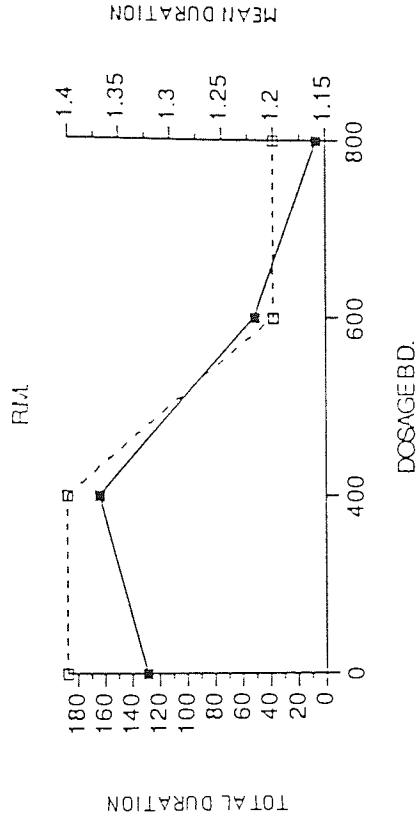
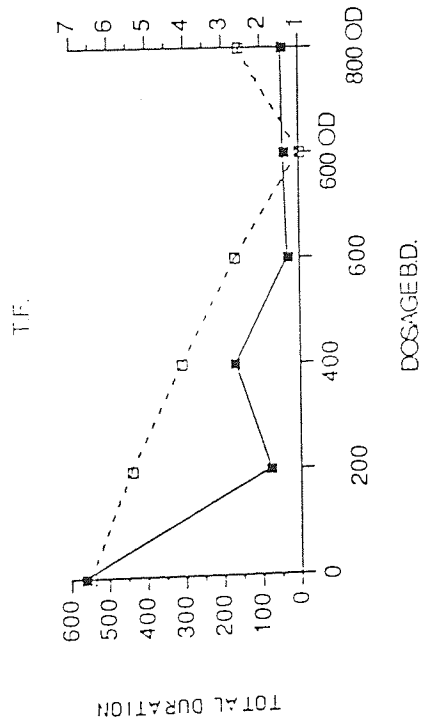


FIGURE 4.6.
RESPONSE TO TREATMENT OF 4 SUBJECTS ON BD WHOSE MEAN
AND TOTAL DISCHARGE DURATION DECREASED.

A comparison of the two regimes

As shown in Table 4.10 the alteration in the number of discharges when patients were changed over was only slight. A t test for related samples in these 6 subjects in fact revealed no significant difference between the percentage reduction in discharges for the initial regime compared to the final regime.

At the end of the study 6 patients were receiving BD sodium valproate, 10 were receiving OD, 3 had been withdrawn and 1 lost to follow-up (Table 4.11).

T tests for independent samples were carried out on the final body weight to dosage ratio and the final percentage reduction in spike and wave activity, to determine whether there was any difference between the two regimes (Tables 4.12a and b). Results showed no significant difference on either measure. For OD the mean dosage to body weight ratio was 25.5 ± 7.1 mg/kg and for BD 19.2 ± 7.8 mg/kg. Although a large difference is reflected in the means this was due to the fact that one patient in the BD group (M.Na) required 38 mg/kg whereas one patient in the BD group required only 8.3 mg/kg.

For OD the mean percentage reduction in spike and wave was $99 \pm 2.5\%$ and for BD $98 \pm 2.4\%$.

The final regime and amount of remaining abnormality in

TABLE 4.10

PERCENTAGE REDUCTION IN TOTAL SPIKE & WAVE
ACTIVITY IN PATIENTS WHO WERE CHANGED OVER

	<u>B.D</u>	to	<u>O.D</u>
J.P	95.5		100
P.J	31.5		100
T.F	95		92
	<u>O.D</u>	to	<u>B.D</u>
S.J	86		100
K.S	97.7		100
M.Na	93		98.6
mean	83.1		98.4
S.D	25.6		3.2

$t = -1.41, df = 5$ not significant

TABLE 4.11 FINAL REGIME FOR EACH PATIENT

Patient	Initial Regime	Final Regime
K.S	OD	BD (slightly improved)
E.C	OD	OD
M.M	OD	OD
M.N	OD	OD
L.B	OD	OD
S.J	OD	OD
J.G	OD	withdrawn
J.T	OD	OD
MNa	OD	BD (improvement)
S.P	OD	OD
S.B	BD	BD
L.E	BD	withdrawn
J.P	BD	OD (improved)
J.O	BD	BD
R.M	BD	OD (improved on lower dose)
P.J	BD	withdrawn
J.Ga	BD	BD
D.B	BD	OD (slightly worse but P.S.better)
T.F	BD	lost to follow-up
C.M	BD	

P.S. = photosensitivity

TABLE 4.12a)

COMPARISON BETWEEN REGIMES OF FINAL
DOSAGE TO BODY WEIGHT RATIO

	<u>O.D</u>	<u>B.D</u>
	28.3	22.6
	16.4	18
	17	25
	20.4	21
	26.8	28.6
	8.3	38
	32.7	
	17.4	
	13.3	
	11.9	
Mean	19.2	25.5
S.D	7.8	7.1

$t = 1.62, df = 14$ (not significant)

TABLE 4.12b)

COMPARISON BETWEEN REGIMES OF FINAL
PERCENTAGE REDUCTION IN DISCHARGES

	<u>O.D</u>	<u>B.D</u>
	100	99.5
	100	100
	100	94
	100	100
	100	100
	98	98.5
	99.5	
	100	
	100	
	92	
Mean	99	98.7
S.D	2.5	2.4

$t = 0.22, df = 14$ (not significant)

each patient is shown in Table 4.13.

The initial amount of spike and wave activity compared to the final dosage necessary to control discharges

In order to ascertain whether a higher dosage of sodium valproate was necessary in patients with greater abnormality, the final mg/kg of sodium valproate for each patient was compared to the initial total duration of discharges. A Spearman's rank correlation coefficient (Siegel 1956) was carried out on the data shown in Table 4.14. Results showed a weak positive correlation between the two sets of parameters ($r_s = 0.38$). Results are plotted in Figure 4.7. This table includes all subjects except the 3 who were withdrawn from treatment.

The number of discharges was then correlated with the dosage required to achieve control and this showed a positive correlation ($r_s = 0.56$) which was significant at the .02 level (Figures 4.8a and b) (Table 4.14).

Pattern of response to treatment

In order to measure the pattern of response to treatment in the event of differences between regimes existing prior to complete control, regression analysis was performed on the mg/kg sodium valproate and the percentage reduction in abnormality for each treatment condition in each subject individually. Unfortunately, due to the

TABLE 4.13

FINAL AMOUNT OF SPIKE & WAVE REMAINING COMPARED TO INITIAL
AMOUNT AND FINAL DOSAGE OF EACH PATIENT

<u>Patient</u>	<u>Total spike/wave initially (secs)</u>	<u>Total remaining (secs)</u>	<u>Dosage (mg)</u>
K.S	838	0	1000 BD
E.C	667	0	1000 OD
M.M	332	0	600 OD
M.N	478	0	400 OD
L.B	373.5	0	600 OD
S.J	952	0	400 OD
J.G*	67	37	800 OD
J.T	120	2	500 OD
M.Na	808	11.5	3500 BD
S.P	971	6 (number)	1500 OD

TABLE 4.13 (con'td)

FINAL AMOUNT OF SPIKE & WAVE REMAINING COMPARED TO INITIAL
AMOUNT AND FINAL DOSAGE OF EACH PATIENT

<u>Patient</u>	<u>Total spike/wave initially (secs)</u>	<u>Total remaining (secs)</u>	<u>Dosage (mg)</u>
S.B	613	0	800 BD
L.E*	926	298	800 BD (syrup)
J.P	742	0	800 OD
J.O	494	0	800 BD
R.M	128.5	8	800 BD
P.J	292	0	200 OD
J.Ga *	75	2	600 BD
D.B	415	0	600 BD
T.F	565	47	800 OD
C.M*	734	42	1000 BD

* = withdrawn or lost to follow-up

TABLE 4.14

INITIAL AMOUNT OF SPIKE & WAVE ACTIVITY
COMPARED TO FINAL DOSAGE REQUIRED
TO ACHIEVE CONTROL

<u>Total duration of discharges</u>	<u>Number of discharges</u>	<u>mg/kg sodium valproate</u>
838	93	29
667	90	28
332	23	16
478	27	17
374	114	17
952	28	13
120	67	12
808	197	38
971	971	19
613	37	23
742	52	27
494	46	18
129	95	25
292	20	7
75	29	25
415	83	21
565	87	33
Mean 521.5	121.1	21.6
SD 283.8	223.5	8

Spearman's Correlation Coefficient

Total duration & mg/kg sodium valproate = 0.38 (not sig.)

mg/kg sodium valproate = 0.56
 at 0.02 level)

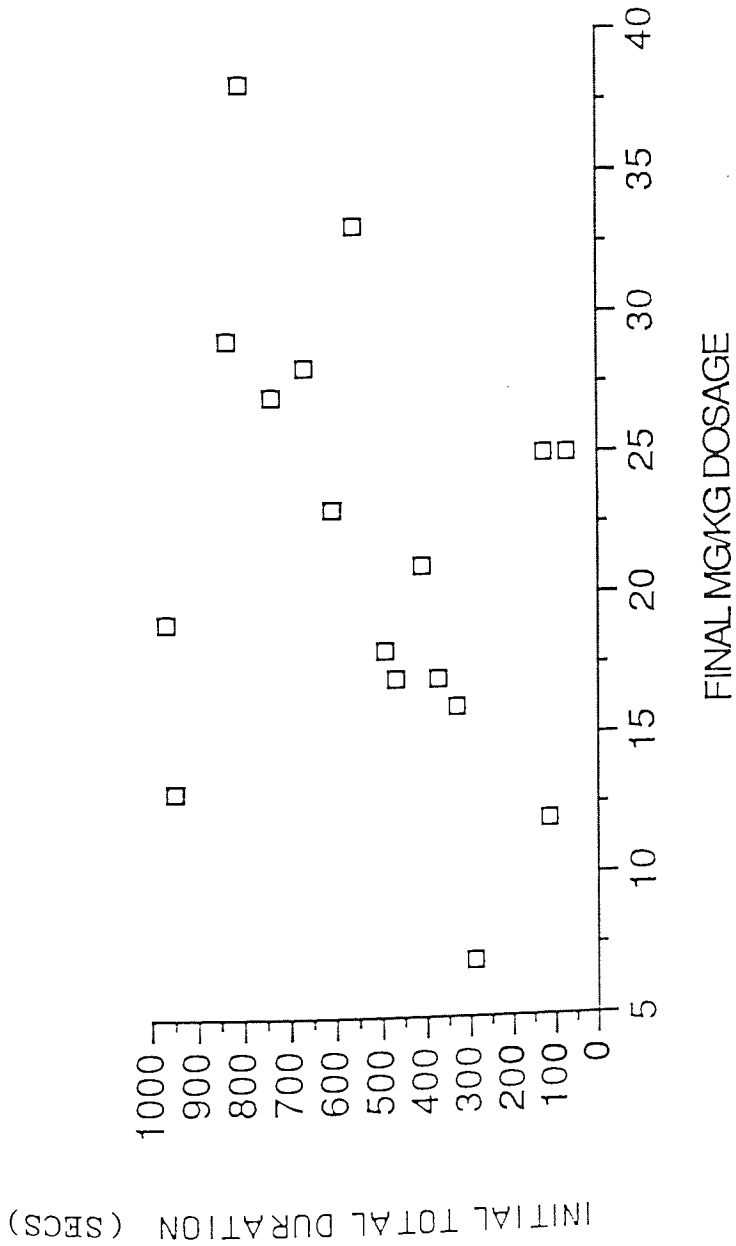


FIGURE 4.7

SCATTERGRAM SHOWING THE RELATIONSHIP BETWEEN THE FINAL DOSAGE OF SODIUM VALPROATE AND THE INITIAL TOTAL DURATION OF DISCHARGES.

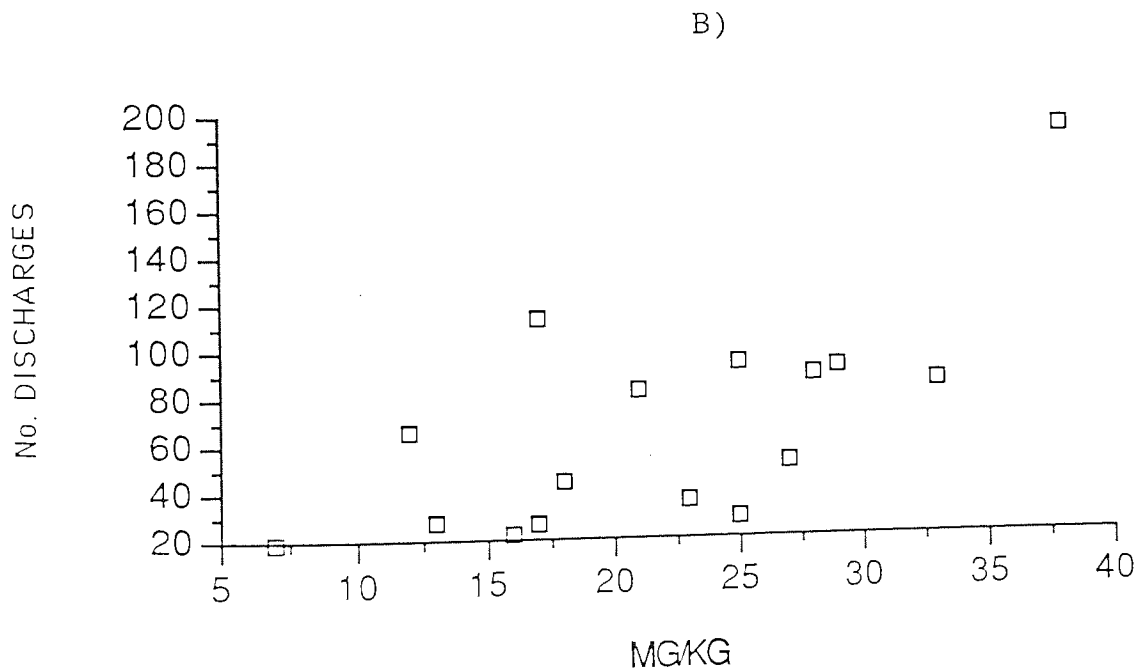
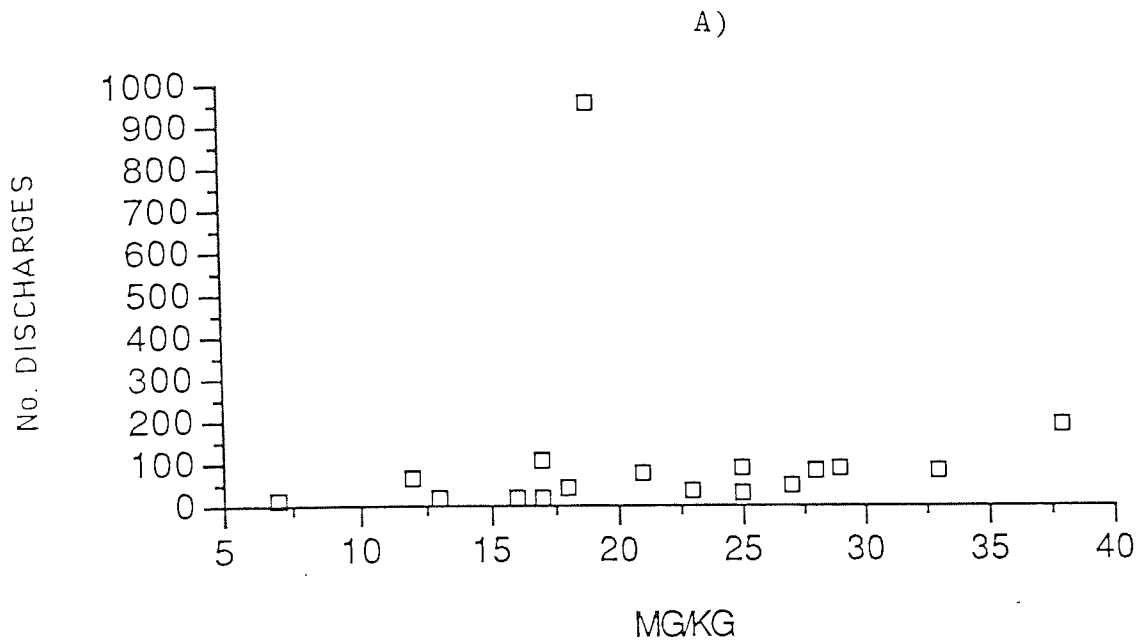


FIGURE 4.8

SCATTERGRAM SHOWING THE RELATIONSHIP BETWEEN THE FINAL DOSAGE OF SODIUM VALPROATE AND THE INITIAL NUMBER OF DISCHARGES A) INCLUDING ONE HIGH SCORER B) EXCLUDING ONE HIGH SCORER

wide range of body weights and dosages it was impossible to match subjects across treatment conditions, such analysis would inevitably require larger patient numbers.

Responses to treatment can be seen in the scattergrams in Figures 4.9 and the results of regression analysis are given in Table 4.15. Visual analysis suggested that some patients showed a curved distribution similar to a logarithmic function and therefore the percentage data was converted to logarithmic values and a simple regression analysis was carried out using a "Statworks" statistical package for the Apple Macintosh micro computer. Unfortunately, 3 subjects had to be excluded due to insufficient data points.

Results showed that in all subjects but 6, the relationship between mg/kg dosage and percentage reduction closely resembled a logarithmic curve. In 4 of these, the first drug increment showed no reduction in discharges from baseline values.

In order to ascertain whether a linear relationship might be more appropriate for all subjects including the six non-significant ones a simple regression analysis was performed on the raw data. This showed that in all subjects tested but one (S.P), a linear regression was a better fit than a logarithmic function and in S.P a linear function was also appropriate. Subject M.Na) would fit either a linear function or logarithmic function equally as well.

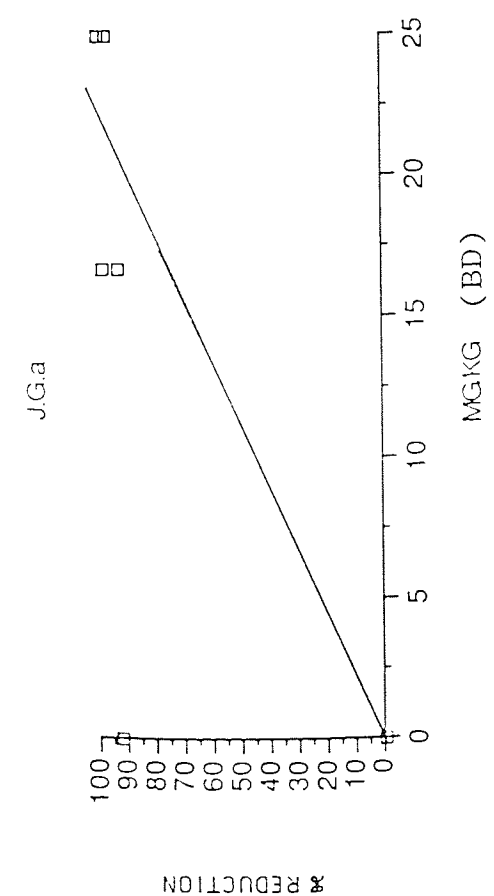
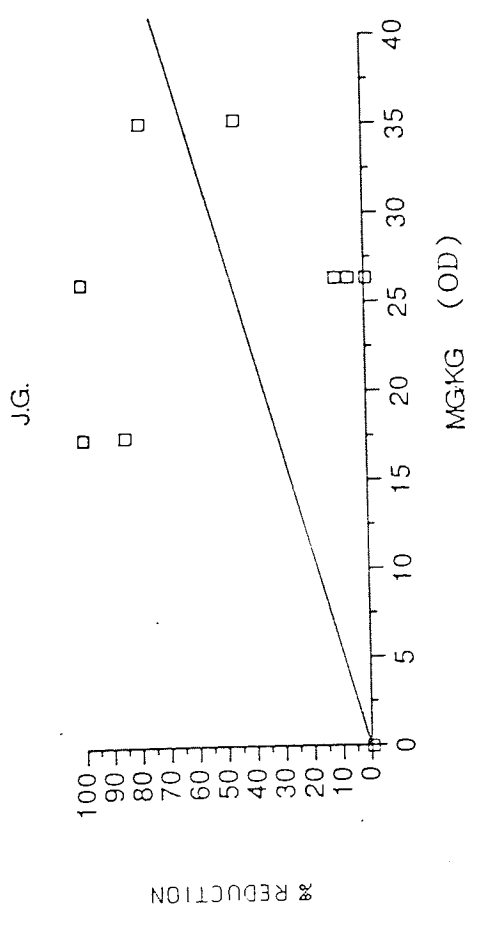
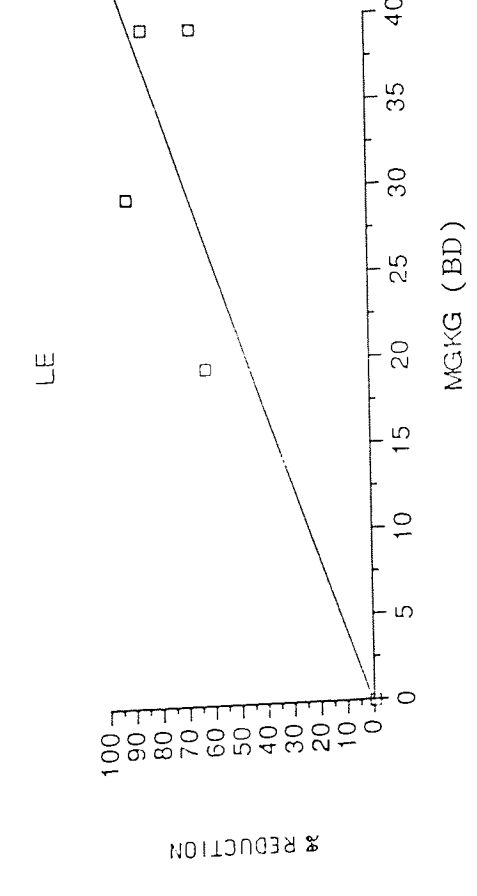
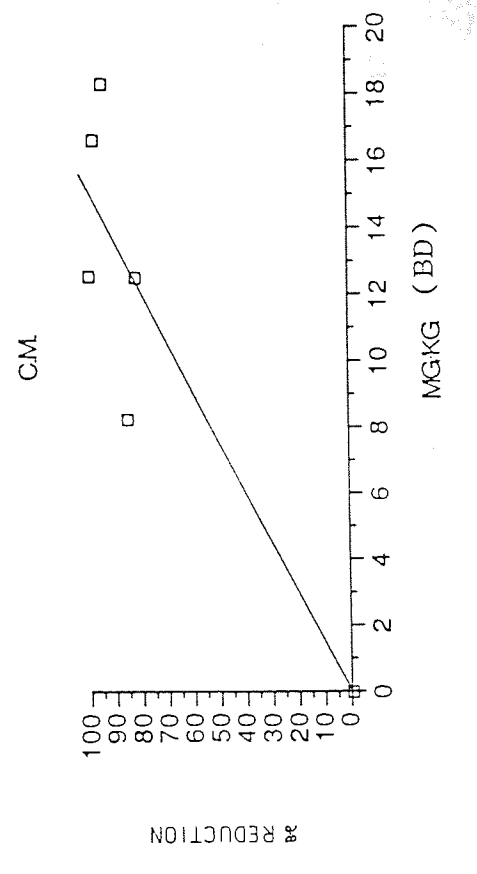


FIGURE 4.9

INDIVIDUAL RESPONSE TO SODIUM VALPROATE AND PERCENTAGE
REDUCTION IN SPIKE AND WAVE, SHOWING REGRESSION LINES.



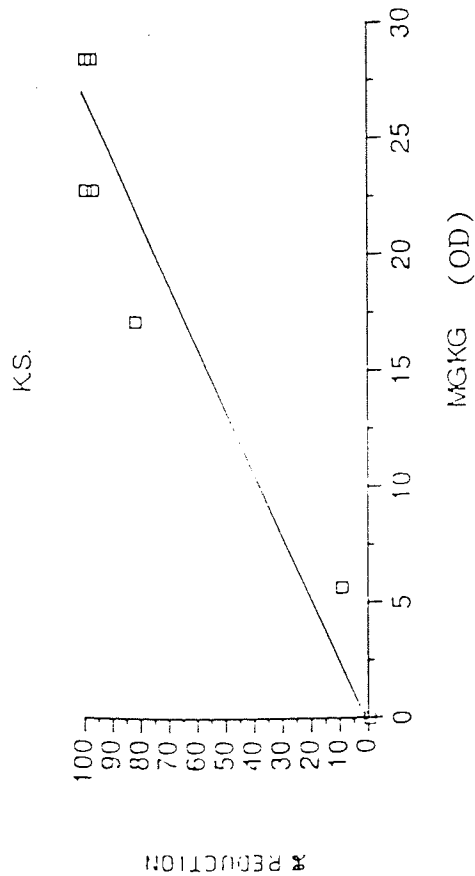
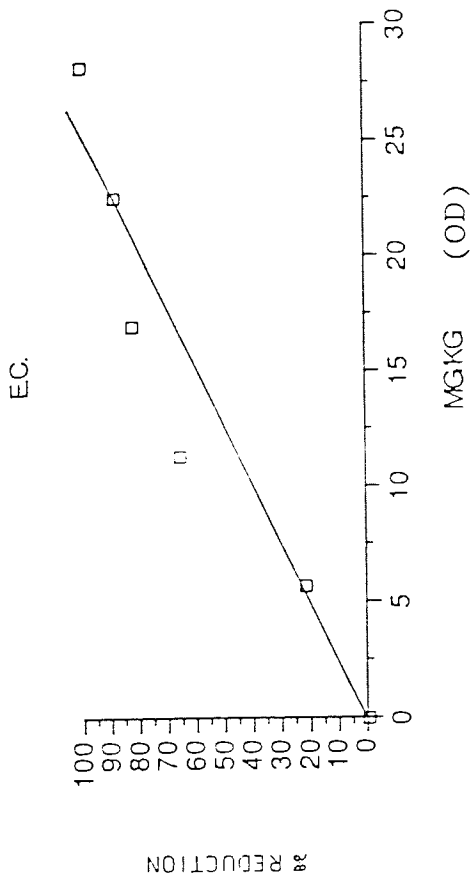
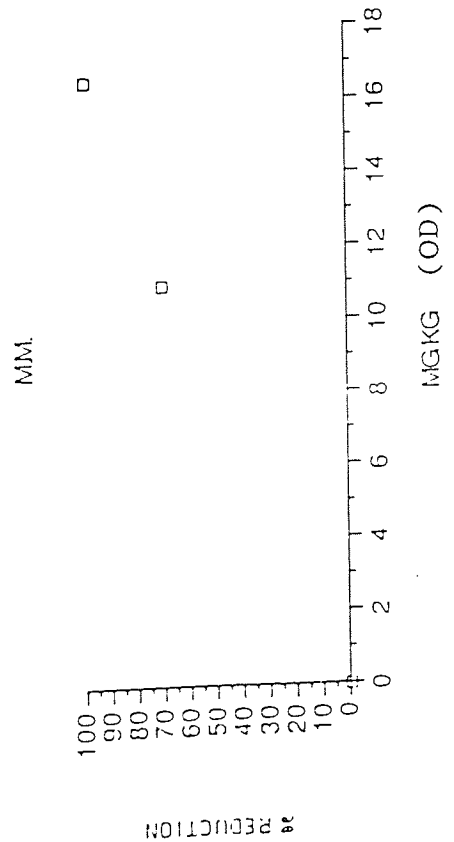
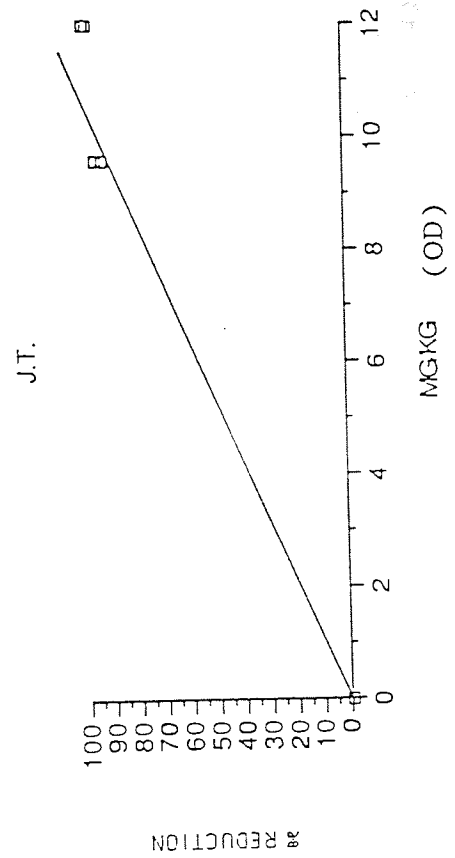


FIGURE 4.9 (continued)



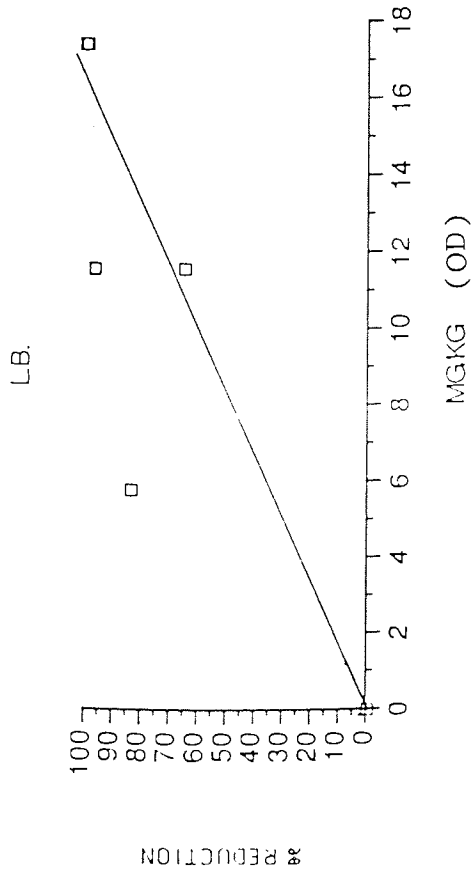
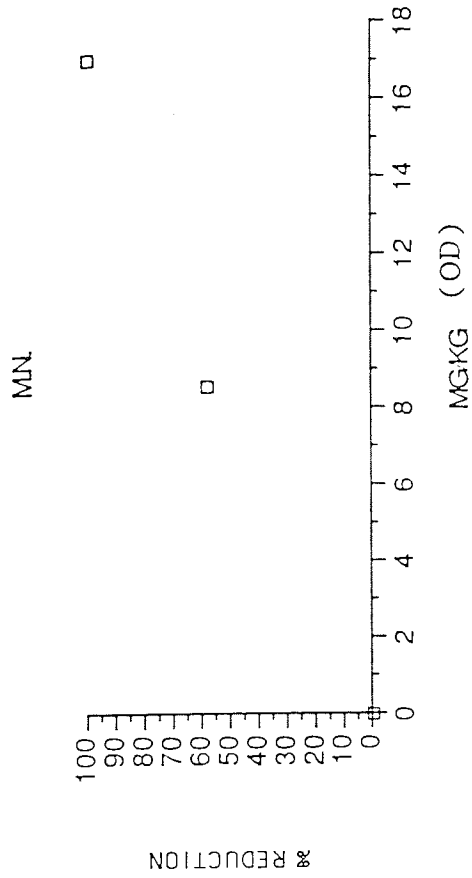
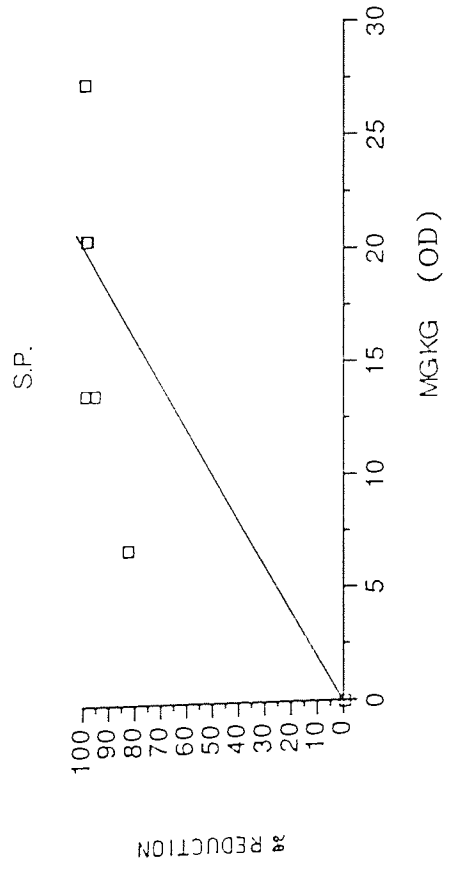
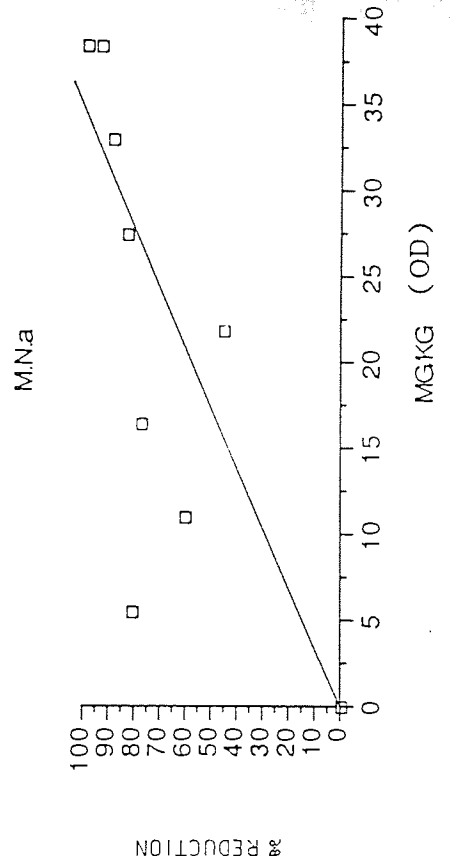


FIGURE 4.9 (continued)



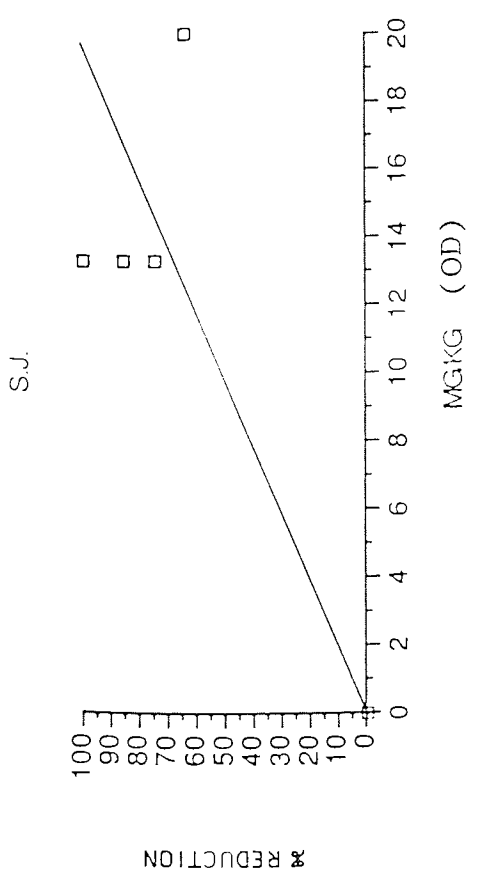
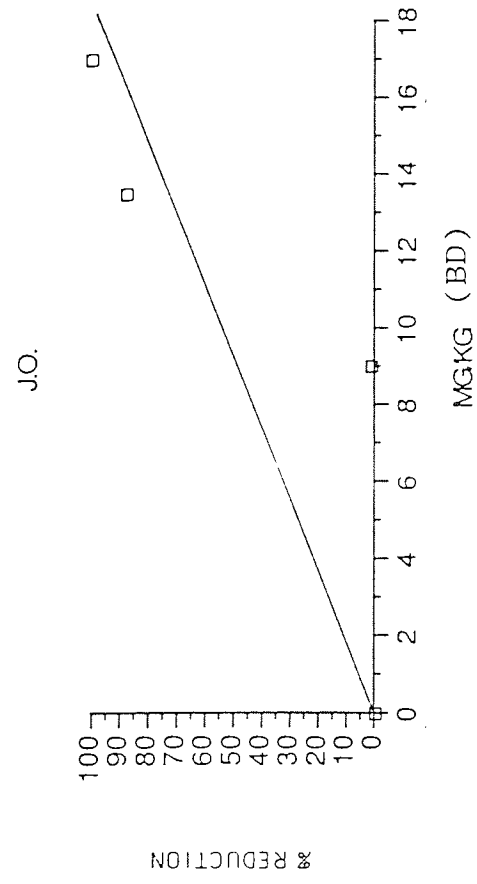
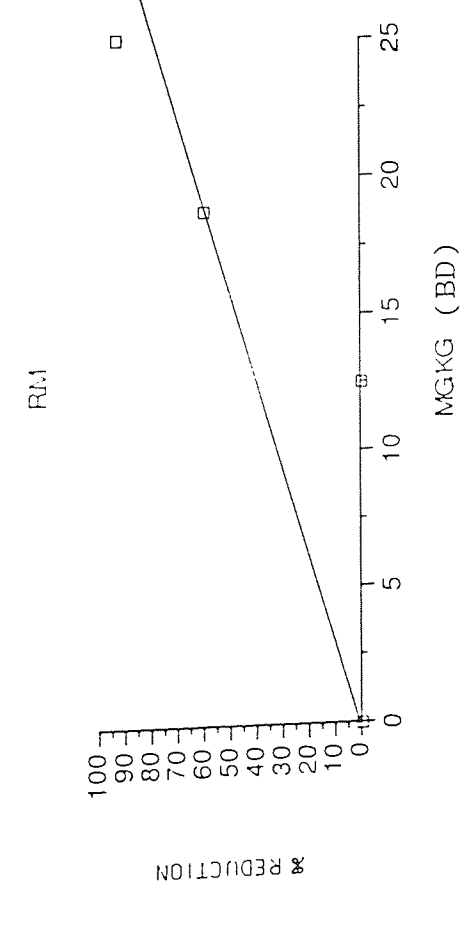
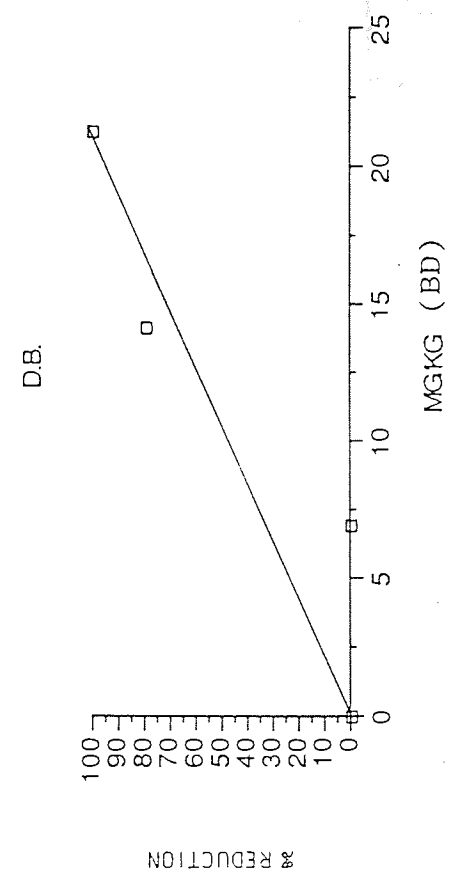


FIGURE 4.9 (continued)



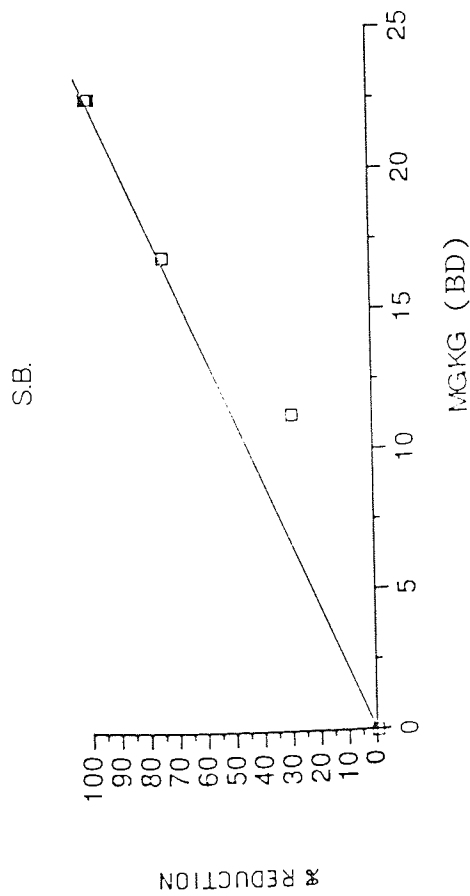
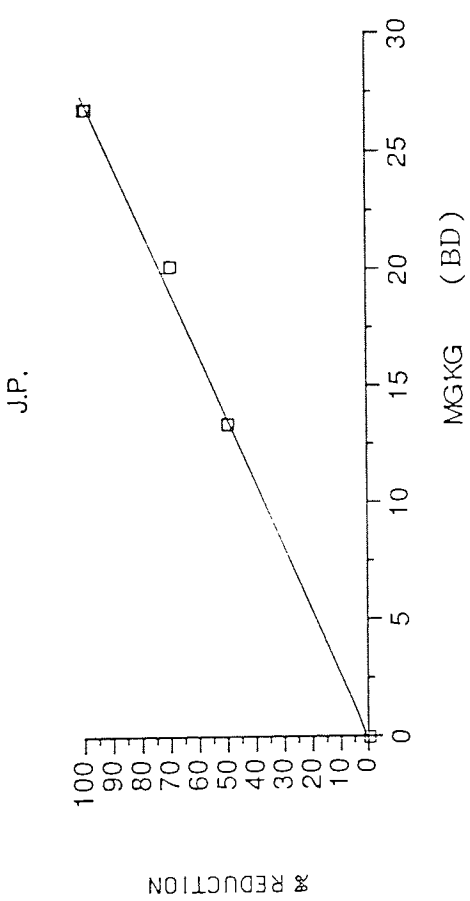


FIGURE 4.9 (continued)

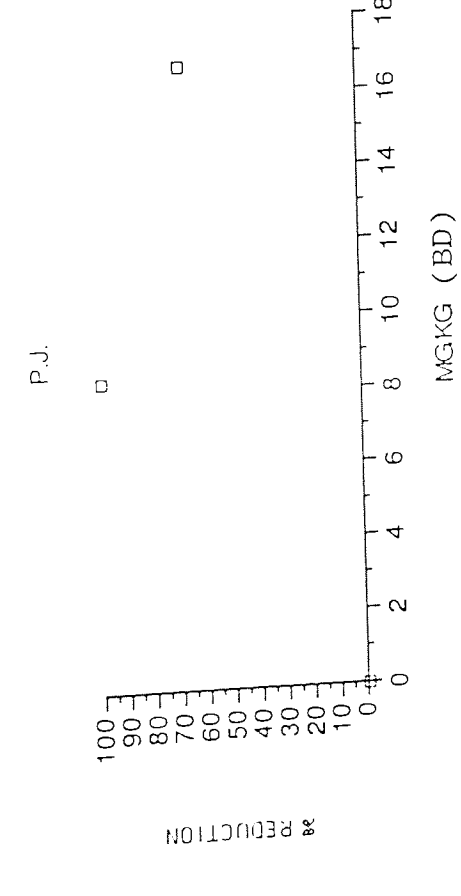
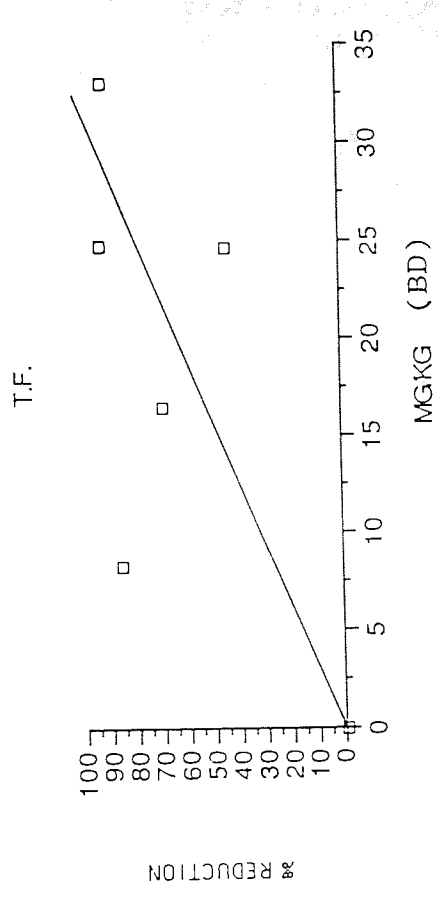


TABLE 4.15

RESULTS OF REGRESSION ANALYSIS OF mg/kg SODIUM
VALPROATE & PERCENTAGE REDUCTION
IN SPIKE & WAVE ACTIVITY

Patient	Regime	Coefficient	t statistic	probability	type of regression
KS	OD	-0.13	-8.66	0.003	log
		3.74	20.88	0	L
EC	OD	-0.10	-15.86	0.001	log
		3.88	14.37	0	L
LB	OD	-0.13	-2.84	0.105	log *
		4.7	3.63	0.015	L
SJ	OD	-0.09	-3.06	0.092	log
		5.10	5.08	0.015	L
JG	OD	-0.02	-1.83	0.117	log *
		1.82	3.21	0.011	L
SP	OD	-0.23	-13.91	0	log
		5.01	6.78	0.001	L
Mna	OD	-0.08	-7.04	0	log
		2.83	6.79	0	L

TABLE 4.15 (continued)

Patient	Regime	Coefficient	t statistic	probability	type of regression
J.T	O.D	-0.32	-16.8	0.004	log
		8.94	20.21	0	L
M.M	O.D	insufficient data points			
M.N	O.D	insufficient data points			
S.B	B.D	-0.16	-4.28	0.023	log
		4.27	18.91	0	L
L.E	B.D	-0.05	-4.29	0.023	log
		2.31	6.96	0.006	L
J.P	B.D	-0.13	-2.84	0.105	log *
		3.70	100.24	0	L
J.O	B.D	-0.11	-1.52	0.37	log *
		5.47	5.42	0.012	L
R.M	B.D	-0.08	-2.61	0.121	log *
		3.06	3.47	0.074	L

TABLE 4.15 (continued)

Patient	Regime	Coefficient	t statistic	probability	type of regression
J.Ga)	B.D	-0.17	-3.45	0.041	log
		4.37	4.86	0.005	L
D.B	B.D	-0.09	-2.03	0.292	log *
		4.71	7.81	0.004	L
T.F	B.D	-0.08	-3.79	0.019	log
		3.16	4.35	0.012	L
C.M	B.D	-0.18	-8.12	0.004	log
		6.44	8.85	0.001	L
P.J	B.D	insufficient data points			

L = Linear regression

log = Logarithmic function

* = not significant

Although the coefficients varied from 1.82 to 8.94 there was no apparent difference in the rate of improvement between the OD and BD subjects (OD mean = 4.38 ± 2.13 , BD mean = 4.17 ± 1.28). Nor was there any difference between the 3 subjects who were withdrawn and those who responded well.

Response of patients who showed photosensitivity

Prior to treatment, 5 subjects showed evidence of photosensitivity. In 3, photosensitivity was abolished at the same dosage at which control of spontaneous discharges was achieved. In patient J.T the dosage at which control of spontaneous discharges was obtained (500mg OD) was doubled before all evidence of photosensitivity disappeared from the basic EEG. Subject T.F was extremely photosensitive prior to treatment (from 1 flash per second) and although the photosensitive range was reduced to 8 to 19fps complete control was not achieved. This subject also continued to show brief spike and wave discharges of less than 1 second duration in the background EEG. Unfortunately, the final photosensitive patient (C.M) was lost to follow up.

Response of patients with tonic-clonic seizures

No child developed tonic-clonic seizures after the onset of treatment or to our knowledge has experienced any since. Of the two subjects with a previous history of tonic-clonic seizures one experienced an attack (K.S)

at 22.9mg/kg, although spontaneous discharges had fallen from a total of 838 seconds to only 21 seconds. The final dosage required to control all discharges was 28.6mg/kg (1000mg BD). In the other patient (L.B) spontaneous discharges were abolished at only 17.4mg/kg (600mg OD) and to our knowledge no further tonic-clonic seizures have occurred.

Clinical attacks

It should be stressed that the monitoring of attacks during this study was purely incidental. Neither patients or observers were asked to particularly look out for events but only to press the event button if an attack happened to be observed. Apart from the obvious problems with ensuring control over such a procedure, this would also have detracted from the patient's normal daily routine. In this study therefore, conclusions can only be drawn about those attacks which were noticed, no claims can be made about those which were not. It should also be noted that although attacks may not have been observed on recording days, it is possible that attacks had been noticed on other days. The study therefore is not meant to be a means of assessing the value of parent observation versus the ambulatory EEG.

In 8 subjects no attacks at all were noted during recording days although in most (see Table 4.3 and 4.4) they had been noted in the past. In one subject (E.C) several attacks were observed but due to malfunction of the 3

TABLE 4.16

DETAILS OF CLINICAL ATTACKS OBSERVED

<u>Patient</u>	<u>Percentage noticed during baseline</u>	<u>Percentage reduction at which last attack was noticed</u>	<u>Shortest duration of event noticed</u>	<u>Number of mistaken events</u>
M.M	21.7	0	13	-
E.C	7.8	88.9	-	-
K.S	8.6	76.7	5	2
M.N	14.8	0	17	-
C.M	6.5	91.3	12	-
D.B	15.7	0	3	1
M.Na)	6.1	83.2	3.5	-
J.O	8.7	21.7	6	-
J.P	11.5	57.7	13	1
S.B	8.1	0	10	3
S.J	10.7	71.4	10	-
L.B	8.8	89.9	3	-
Mean	10.75	48.4		
S.D	4.57	40.7		

TABLE 4.17

COMPARISON OF MEAN DURATION OF NOTICED
ATTACKS & ACTUAL MEAN DURATION

<u>Patient</u>	<u>Mean duration of noticed attacks</u>	<u>Actual mean duration of all discharges</u>
S.J	21	22.9
L.B	3.4	3.4
M.M	14.6	14
K.S	8.6	7.8
J.O	10	10.7
J.P	16.4	16.6
S.B	17.7	17
M.N	17.8	17.7
C.M	17.6	13.2
D.B	5.4	5
M.Na	4.9	4.6

channel recorder the 4 channel EEG recorder was used. Therefore, there was no event marker and it was not possible to assess the duration of events, only the number noted. Table 4.16 shows these results.

It can be seen from the first column that during the baseline recording between 6 and 22% of attacks were noticed (mean 10.8%). From the second column it can be seen that in 4 patients with zero reduction no further attacks were noted after the baseline recording. Of the remaining patients it is evident that in several, attacks were still being observed even after discharges had been reduced by up to 91% (mean 48.4 ± 40.7). In 7 cases observers pressed the event button and noted an attack but were mistaken.

Table 4.17 compares the overall mean duration of observed events to the actual EEG mean duration on the same recording days. Apart from one subject (C.M) these values are very similar. Therefore it would seem that observation was not necessarily restricted to the longer attacks. The shortest attack noticed in individual subjects varied from 3 to 13 seconds (mean 8.7 ± 4.8 seconds).

Conclusion

Baseline recordings showed a great deal of inter and intra-subject variation suggesting not only that a short basic EEG is unrepresentative but that even 24 hours may be inadequate. Results were similar to those of Binnie et al.

(1982) showing that the mean duration of discharges was more stable than the total duration.

The need to treat these patients as soon as possible is highlighted by the fact that in most subjects the total time occupied by discharges was over 100 seconds and in 10 patients it exceeded 8 minutes. In most patients the mean duration of discharges exceeded 3 seconds suggesting that cognitive impairment was extremely likely (Penry 1973). Findings also confirm those of other authors that absence seizures last for an average of 10 seconds.

Although patients with briefer discharges did tend to experience more attacks, no inferences about the total duration could be made from the mean. However, there are possible implications about seizure production. Stevens et al. (1971) have suggested that there may be a build up of a substance which requires release. Present findings would suggest that in some patients an initial build up is followed by a rapid release whereas in other patients there is a longer build up and longer dissipation. This would also obviously depend on the intervals between discharges which are discussed in Chapter 5.

The next question asked was; do patients with more frequent, briefer discharges require the same amount of medication as patients with fewer, longer discharges?

The final dosage required to control discharges showed no correlation with the total duration of discharges but did correlate with the number of discharges, suggesting that patients with more discharges required more medication. As these patients were often also the ones with briefer discharges it may follow that short, frequent discharges are more difficult to control than long discharges. This therefore explains the finding of Stefan et al. (1984) who showed that discharges of longer duration were abolished earlier. This is also illustrated by patient T.F in whom we were able to drastically reduce discharges of longer than 1 second but several briefer discharges remained, even on a dose of 33mg/kg.

The response to treatment was as expected except in one subject who showed an erratic response, one who failed to respond and 2 whose parents reduced the medication and brought about improvement. In one of these patients there was a change in family circumstances illustrating how the environment can affect the number of attacks. In another patient, discharges increased during menstruation. None of the other female patients had reached their menarche.

There were three individual response patterns to treatment:

1. The mean duration of discharges increased initially (7 cases)

2. The mean duration of discharges reduced, though to a lesser degree than the total duration (5 cases)
3. The response of the mean and total duration was the same (8 cases)

There was no obvious difference between the three groups on age, weight, sex, frequency of spike and wave, clinical signs, amount of abnormality or final dosage of sodium valproate. The reason for the 3 types therefore remains uncertain. The slower reduction in the mean duration of discharges is in keeping with the findings of Stefan et al. (1984).

In 14 subjects, two final recordings were carried out at the same dosage to ensure that results were reliable. In 7 subjects both recordings showed no discharges. In 4 subjects the number of discharges increased and in 2 the number of discharges decreased slightly. There is no evidence therefore to suggest a delayed effect in this study although the experimental design may itself have excluded this possibility.

In the one subject who experienced a tonic-clonic seizure almost all discharges had been abolished and there were no discharges on a second days recording at the same dosage. This therefore supports the assumption that a normal EEG can be found in patients with tonic-clonic

seizures (Gastaut and Broughton 1972).

The comparison between the percentage reduction of spike and wave and the amount of drug required to achieve control showed no significant difference between the two regimes. Even in subjects who were changed over, the change in response was so small that there was no significant difference between the amount of abnormality on the initial or final regime. These findings do not therefore support the findings of Covanis, Jeavons and Gupta (1981) that a single large dose of valproate may be more effective than a divided dose. They do however, suggest that a single dose is equally as effective as a divided dose.

It was possible that these findings occurred because comparison was only made at a high degree of control and that differences would only be observed at lower, less effective dosages. However, the response to treatment was found to be linear in both OD and BD regimes and there was no difference between the two sets of coefficients. It could possibly have been argued that a tendency towards a steeper regression in one group suggested that this was effective earlier, but no such pattern was found. The pattern of response to treatment was therefore also the same for the two regimes. Of the 5 patients remaining in the study who were photosensitive, only one required an increase in dosage above

that which abolished spontaneous discharges. In one other patient neither photosensitivity or all spontaneous discharges were abolished. There is therefore little evidence to suggest that these patients were more difficult to control (the mean dosage was $22.8\text{mg/kg} \pm 8.6$).

The overall mean dosage for all patients was 21.6mg/kg which is slightly higher than Stefan et al. (1984). Side effects were still minimal, one subject developing a tremor which appeared to be dose related (33mg/kg), in one female there was weight gain and in one child there was drowsiness. The same subject who experienced tremor also showed transient hair loss. None of these effects appeared to be related to a particular regime.

The analysis of observed clinical events was difficult as the study was not designed to examine this. It appears however, that on a normal day either the parents or the child noticed between 6 and 22% of attacks only. Blomquist and Zetterlund (1985) found that parents noticed around 10% of attacks. On average, attacks were no longer noticed after the actual duration of discharges was reduced by 50%.

These findings would therefore not support the view of Blomquist and Zetterlund (1985) that parental observation is superior to the EEG in diagnosing control. The fact that several events were noted which were not actually associated with seizure discharges is also against this hypothesis.

The shortest discharge which was clinically noticeable was 3 seconds thus supporting the view of Penry (1973) that discharges of 3 seconds and over may show overt signs. As the mean duration of discharges noticed was similar to the actual mean duration it would appear that it is not simply longer discharges which are noticed. As suggested by Penry this may be more associated with activities, at the time of the attack, which are interrupted.

In summary, ambulatory monitoring has shown, as indicated by Stefan et al. (1984) that it can be used to fine tune the dosage so that the minimum amount of drug was given. Some subjects required a surprisingly low dose as little as 8mg/kg. There is still a problem of day to day variation however, which suggests that 48 hour recording may be required to ensure that complete control is reliable.

It has been shown that sodium valproate can be given in a single dose at night and is equally as effective as a divided dose. There were no problems with compliance in subjects on either a divided or single dose as far as we know. There were no adverse effects requiring withdrawal of the drug except in one child who became drowsy in class and was taken off all medication without unfavourable consequences. Only one child failed to respond totally, although discharges were reduced by around 50%. In this patient ethosuximide completely abolished discharges.

In general therefore, sodium valproate is highly effective in patients with absence seizures and is equally as effective when given once or twice daily. However, many parents and patients find once daily administration more convenient. It was shown by Covanis et al. (1982) that compliance improved with this regime.

CHAPTER 5

CIRCADIAN VARIATIONS IN EPILEPTIC ACTIVITY
IN PATIENTS WITH ABSENCE SEIZURES ON AND OFF
SODIUM VALPROATE

CIRCADIAN VARIATIONS IN EPILEPTIC ACTIVITY IN
PATIENTS WITH ABSENCE SEIZURES ON AND OFF SODIUM
VALPROATE TREATMENT

Introduction

Studies of the rhythmicity of inter-ictal abnormalities or indeed seizures themselves are carried out with a view to elucidating some of the underlying mechanisms involved in seizure production. It has also been suggested that a knowledge of such rhythms could improve the choice of EEG sampling time and the time of drug administration. Ambulatory EEG monitoring is a most appropriate method of evaluating such changes and the patients described in Chapter 4 provided an ideal study group.

One of the reasons for undertaking such a study was that previous reports are often confused and conflicting in that they include patients with various types of epilepsy receiving different anticonvulsants. It was hoped that our more homogenous group of patients who all underwent recordings both prior to and during treatment, might clarify some of the previous findings. Furthermore, if there was no difference between circadian cycles of abnormality in patients on OD sodium valproate and patients on BD, then further weight could be given to the argument that an OD regime is equally as effective as a BD regime despite the relatively short half life of the drug.

The following literature review shows that not only do

due to different methods of sampling and analysis. Most of the data was gathered using radio or cable telemetry on in-patients.

The main contributions in this area come from 4 different groups of authors. The earliest and most frequently cited is that of Stevens, Kodoma, Lonsbury and Mills (1971) who studied 5 patients for a total of 18 days. Two patients had generalised epilepsy and 3 had partial epilepsy. Three of the 5 were receiving A.E.Ds. Much of the analysis concentrates on the relationship between the duration of seizures and the inter-seizure interval. The rest is concerned with the temporal distribution of spiking as measured in either one or 4 minute epochs.

Similar work was carried out by Kellaway, Frost and Crawley (1980). These authors however, studied a more homogenous group of 19 patients with generalised epilepsy for between one and nine days. They looked at the relationship between inter-ictal spiking and the sleep cycle and also at the duration of intervals between spiking in waking and sleep. The analysis was carried out using 15 minute epochs. Most of the patients were not receiving medication.

A large study was carried out by Martins, DaSilva, Aarts, Binnie et al. (1984) using mainly patients with partial seizures who were receiving medication and 5 patients with generalised seizures. A total of 18,24 hour recordings were examined from 17 patients. A rather unsuccessful
activities so

that consistency in the same subjects between days could be measured. Ultimately, only 2 subjects showed significant day to day consistency of daily activities. These authors also examined the distribution of minima and maxima of discharges across time and the intervals between events. Thirty minute epochs were used in the analysis of inter-ictal spiking.

Finally, Binnie, Aarts, Houtkooper et al. (1984) carried out further analysis on some of the patients described by Martins, Da Silva et al. (1984) and also examined seizure records of a group of patients in a 9 month flunarazine trial and seizure calendars of a group of mentally subnormal patients with intractable secondary generalised epilepsy.

Already several differences in design have emerged, eg. the type of patient studied, whether or not medication was being given, the epoch length of the parameter studied and the parameter itself, eg. temporal distribution of seizures or intervals between peaks of inter-ictal spiking.

In addition, the analysis employed by different authors and the interpretations placed on seemingly similar results often conflicts. Firstly, there is disagreement about the presence or absence of an overall circadian rhythm in the incidence of discharges. Kellaway et al. (1980) propose a theoretical model of two superimposed

cycles one of 24 hours and one of approximately 100 minutes. The peak of the longer cycle is found during sleep therefore more spike and wave activity is present in sleep and an underlying rhythmicity due to the 100 minute cycle is evident. If the longer cycle is shifted by 30, 120 or 210 degrees the amount of spiking present at different times of the night will vary although an underlying 100 minute cycle is still present.

Kellaway et al. did in fact demonstrate 3 different patterns of spike occurrence during sleep. During waking the longer cycle is said to be at its lowest and "random noise" is introduced into the theoretical model to account for the fewer random discharges found in their patients during waking.

Martins, Da Silva et al. (1984) reproduced Kellaway et al's. finding of 3 types of patterns during sleep and also an initial increase in spiking at sleep onset in patients with generalised epilepsy only. However, they argue that such patterns may exist at any time of the day when the patient chooses to sleep. This is therefore not a circadian rhythm but an effect secondary to the sleep state. Martins, Da Silva et al. further argue that a lack of significant agreement between subjects in the time of occurrence of spiking would argue against a circadian rhythm. These authors found that on first analysis a significant correlation did exist between or within subjects across the 24 hour period. However,

this was due to the influence of the sleep/wave cycle with most subjects producing more abnormality during sleep. When sleep and waking were analysed separately, no significant correlation was found for waking, but this was found for sleep. Similarly, Binnie et al. (1984) argue that no other rhythm than the sleep/wake cycle was in evidence from their rather more long-term data.

With regard to periodicities, most authors agree that these do exist in some form and vary from between roughly 80 and 120 minutes. Binnie however, found intervals as low as 13 minutes. Stevens et al. (1971) are the only authors to find periodicity to occur to any large extent during waking. During sleep, Kellaway et al. found the periodicities to correlate with the REM cycle but Binnie et al. did not. Martins, Da Silva et al. found that periodicities occurred more often at night and were also more often of longer than 100 minutes in duration at night.

Perhaps the most difficult and most conflicting area of analysis is in the interpretation of the length of intervals between ictal and inter-ictal events. Stevens et al. (1971) argue that if the lengths of intervals between seizures are plotted in a histogram, and form a Poisson distribution with an excess of short intervals then this suggests a low seizure threshold. Coupled with many attacks of short duration, they argue that this implies a steady build up of some substance which requires

discharge. Conversely, Binnie et al. (1984) argue that a Poisson distribution of intervals between events would argue against such a so called "relaxation process", rather it would imply that the duration of intervals was randomly determined with a superimposed rhythmic pacemaker to account for the 13 to 143 minute intervals found in sleep. These authors failed to detect any correlation between inter-discharge or inter-seizure intervals, again suggesting little evidence of a relaxation process.

Strictly speaking, a Poisson process is one in which all events are independent of each other and therefore Binnie et al. are probably more accurate in their interpretation.

Both Martins, Da Silva et al. and Binnie et al. argue for the existence of a "modulated" Poisson process, ie. a random distribution of interval durations but intervals bias towards one particular length occurring at a particular time of day. Martins, Da Silva et al. for example found periods of greater than 100 minutes to occur more often at night.

Finally, perhaps the only area of agreement between authors is the general finding of a lack of significant negative correlation between serum AED levels and inter-ictal epileptic activity. Kellaway et al. also note that in all subjects, fully effective therapy changed previous patterns of spiking during sleep to more random patterns. As the present study was aimed at assessing the effect of

sodium valproate on discharges some discussion of daily variation in serum levels is necessary.

Daily variation in serum level profiles

Binnie et al. (1982) state "if the finding of extreme variability in amount of epileptiform activity is discouraging for those electroencephalographers who seek to correlate quantitative measures of epileptiform activity with drug effects, our pharmacological results may seem yet more perplexing for those clinical chemists who devote their energies to developing pharmacokinetic models". This statement is based on the finding that after examining 130, 48 hour recordings, only 12 patients could be found who exhibited consistent 48 hour serum AED profiles. After long term EEG monitoring of the same 12 patients for 48 hours, and keeping environmental factors as consistent as possible, the day to day variation in EEG abnormality was still very high.

Several authors have examined serum level profiles of valproate in varying formulations and on various patient groups. Few authors unfortunately, have correlated these with effects on EEG discharges.

Results of various serum level studies are shown in Figure 5.1. The peaks in this diagram are a simplified representation of the time of maximum peak serum levels and also one minima obtained by other authors.

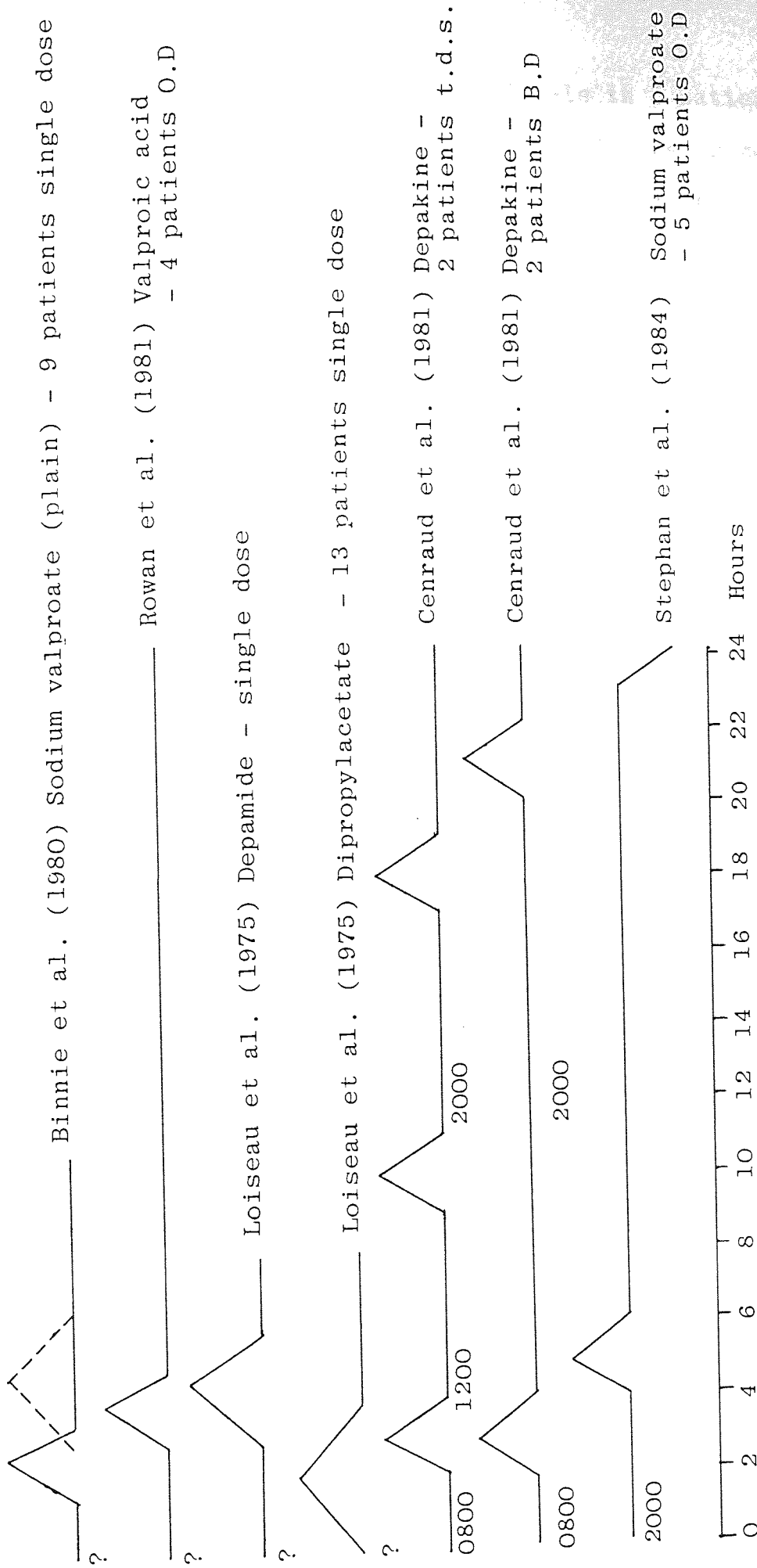


FIGURE 5.1
 DIAGRAMMATICAL REPRESENTATION
 OF TRIALS OF PEAK SERUM LEVELS

Stefan et al. (1984) studied serum levels in 5 patients with absences, tonic-clonic, myoclonic seizures or combinations of these, who were being treated with O.D. sodium valproate enteric coated. Serum levels were ascertained at two hourly intervals. Generally, patients show a fast rise in serum level from 2 hours after administration, peaking between 4 and 6 hours and then falling slowly and steadily until the next evening dose. It is suggested that this implies good penetrance into the brain although the reason for this hypothesis is not clarified.

Cenraud et al. (1981) investigated serum levels in 4 patients receiving Depakine in either a twice daily or three times daily (T.D.S.) regime. On a B.D. regime peaks were found between 2 and 4 hours after the morning dose and 8 to 10 hours after the evening dose. On a T.D.S. regime peaks were found 2 to 4 hours after the morning dose, 5 to 7 hours after the afternoon dose and 5 to 7 hours after the evening dose. They found that in both groups serum levels were closest to the mean between 1600 and 1800 hours and on a T.D.S. regime serum levels showed less fluctuation.

Loiseau et al. (1975) administered a single oral dose of dipropylacetate to 13 patients and always found a peak in serum level by 4 hours after administration. In 3 patients peak levels were found after 1 hour. After a single oral dose of Depamide in 5 patients dipropylacetate reached a maximum in the blood after 3 to 6 hours.

Rowan et al. (1981) estimated serum levels in 4 patients on co-medication who were receiving O.D. valproic acid. Peak serum levels were obtained 3 to 5 hours after administration and then declined slowly.

Binnie et al. (1980) reported one of the few studies which also includes EEG data. In this case the effect of a single oral dose of sodium valproate (Epilim) on the photosensitivity range was examined in 9 subjects naive to sodium valproate and 7 subjects on chronic treatment. All subjects but one showed peak levels within 3 hours of administration and the delay between peak serum level and maximum reduction in the photosensitivity range varied from one to five hours in the 9 subjects who showed any effect, EEG effect is shown by the dotted line in Figure 5.1.

Finally, Burr et al. (1984) studied 7 previously untreated patients with absence seizures. They carried out a baseline ambulatory EEG and another ambulatory EEG on a day of partial control. They attempted to correlate serum levels with the rate of EEG discharges and also allowed for a possible delayed effect by using 12, 2 hour steps of time lag. Despite this no correlation was found between serum level and EEG effect. Unfortunately, they do not give details about the dosage regime, time of drug administration or peak serum levels although from individual patient graphs it would appear that for most patients the highest peak serum levels occurred between 22.00 and 00.00. In most subjects the lowest discharge rate appears to have

occurred between 20.00 and 03.00. although this may be an over-simplification of their data.

In conclusion it would seem that serum level studies are prone to as much diversity in design as studies of daily variations in EEG activity. If one consults Figure 5.1 however, it appears that all peaks in serum levels occurred within 5 hours of a single dose whatever formulation was used and most peaks occurred at 3 hours. In the one study which employed multiple dosage peaks occurred 3, 6 or 9 hours after the last dose depending on the time of day. Results also suggest that peaking is delayed at night.

Unfortunately, serum levels were not carried out in the following study but as the time of drug administration was standardised across each group of subjects, inferences may be made from the findings of other authors if appropriate.

This study examines the circadian distribution in spiking in 10 patients with absences prior to treatment and then after partially effective treatment with sodium valproate administered in either a once or twice-daily regime.

5.2 Method

Patients

Ten children with frequent discharges of generalised spike

and wave were selected from those described in Chapter 4 (M.M., M.N., S.B., J.P., R.M., K.S., J.O., L.B., E.C. and L.E.).

Five children had been allotted to a once daily regime of sodium valproate enteric coated and 5 had been allotted to a twice daily regime. Ages ranged from 6 to 12 years and the mean age was 9.4 ± 2 years for both groups. There were 3 males and 2 females in each group, the mean weight for the O.D. group was 34 ± 5 kg and for the B.D. group 32 ± 9 kg. In most patients the main frequency of the spike and wave was 3cps although two patients in the O.D. group showed a 4cps component and one in the B.D. group showed a 5cps component. Two patients in the O.D. group were photosensitive and two had a history of tonic-clonic seizures. In the B.D. group only one patient showed photosensitivity.

Apparatus

Ambulatory EEG recordings were carried out using 3 EEG channels and one time event channel as described in the method in Chapter 3.

Procedure

The procedure was similar to that described in Chapter 4. However, for this study only 2 recordings from each patient were examined (one baseline and one drug).

Method of Analysis

Tapes were replayed on the P.M.D.12 visual display system. Analysis consisted of counting the number of spikes in each 15 minute epoch. As pointed out by Declerck et al. (1982) there is considerable variation in the morphology of spike and wave activity during sleep, the slow component is often difficult to differentiate from 'K' complexes and sleep delta waves. For this reason spikes only were counted during both waking and sleep. During waking, analysis was relatively simple as discharges were usually prolonged and easy to differentiate by sound. Replay could therefore be carried out at 60 times real time. During sleep however, spiking tended to be briefer, and not as well defined. It was often necessary therefore, to carry out page by page analysis which was very time consuming. Due to the lack of eye movement and submental EMG channels it was felt inappropriate to attempt to score sleep stages. It was not possible therefore to correlate spiking with the sleep stages as defined by Rechtschaffen and Kales (1968).

5.3 Results and statistical analysis

Inter-subject agreement

The first part of the study was to assess consistency of occurrence of spiking across the 24 hour period between subjects. There was a great deal of variation in the amount of spiking present in different subjects. Therefore,

in order to prevent any undue contribution from any individual the data was normalised. This was carried out by entering the raw data into an R.M.L. 380Z microcomputer which divided each number of spikes per epoch by the greatest number of spikes in an epoch for that subject. For the next part of the analysis the data was summed into 90 minute epochs.

The statistical test used was Kendall's Coefficient of Concordance (Siegel 1956). Results of this analysis can be seen in Table 5.1a. Significant agreement was found at the 5% level between all subjects across the 24 hour period. However, when waking and sleep were analysed separately, only the sleep data showed significant agreement at the 1% level. Results are plotted in Figure 5.2. The mean waking and sleep onset times are shown on the graph and the actual mean values and the standard deviations for each 90 minute epoch are given in Table 5.2. It can be seen that spiking falls to a minimum between 22.30 hours and 03.00 hours. Maximum values are seen on waking and sleep onset.

Next the effect of sodium valproate on the above pattern was examined. First of all it was necessary to select one recording from each subject during which partial control had been achieved from recordings described in Chapter 4.

A criterion of a 50% or more reduction in spike and wave activity during waking was used. In order to ensure that

TABLE 5.1a

RESULTS OF KENDALL'S COEFFICIENT OF CONCORDANCEFOR AGREEMENT BETWEEN SUBJECTS

Parameter	Number of 90 min. epochs	W value	d.f.	X ² value	Sig. level
All subjects 24 hours Baseline	16	0.18	15	26	.05*
All subjects waking only Baseline	10	0.1	9	8.73	0.5
All subjects sleep only Baseline	6	0.45	-	781(S)	.01*

TABLE 5.1b

OD subjects 24 hours Drug	16	0.18	15	13.5	.7
BD subjects 24 hours Drug	16	0.13	15	9.75	0.9

* = significant

FIGURE 5.2 MEAN NUMBER OF SPIKES (NORMALISED) PER 90 MINUTE EPOCH FOR ALL SUBJECTS ACCORDING TO TIME OF DAY

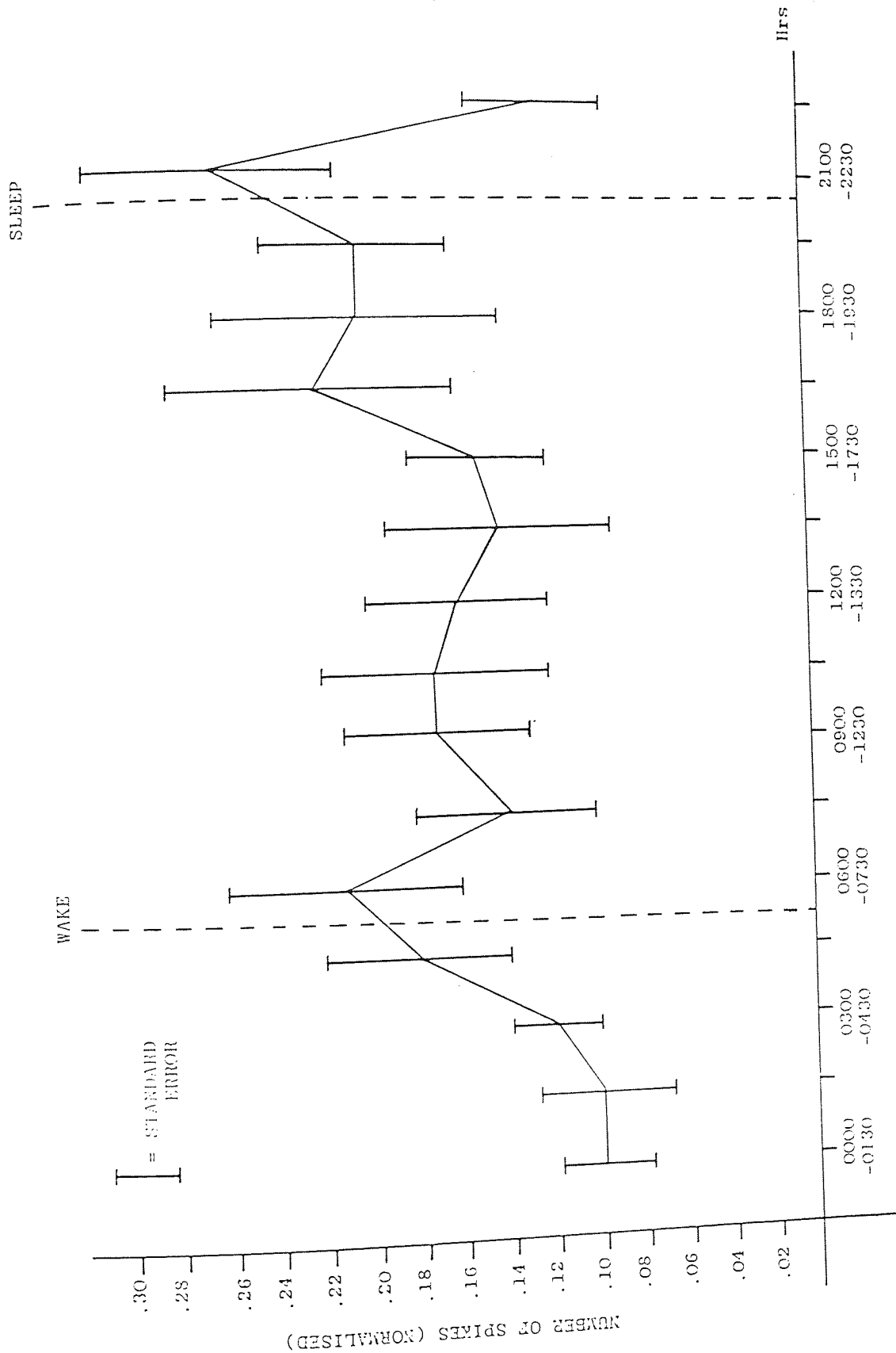


TABLE 5.2

MEANS AND STANDARD DEVIATIONS FOR EACH
90 MINUTE EPOCH PLOTTED IN BASELINE GRAPH (FIGURE 5.2)

<u>TIME</u>	<u>MEAN</u>	<u>STANDARD DEVIATION</u>
0000-0130	.10	.05
0130-0300	.10	.07
0300-0430	.12	.07
0430-0600	.18	.12
0600-0730	.21	.16
0730-0900	.14	.12
0900-1030	.17	.11
1030-1200	.17	.15
1200-1330	.16	.11
1330-1500	.14	.16
1500-1630	.15	.09
1630-1800	.22	.18
1800-1930	.20	.18
1930-2100	.20	.13
2100-2230	.26	.15
2230-0000	.13	.09

there was no bias in the sampling process a Mann Whitney U Test (Meddes 1975) was carried out and showed no significant difference between the 2 groups in the percentage reduction of spike and wave activity. On B.D. the mean reduction was $68 \pm 15\%$ and on O.D. $76 \pm 12\%$. There was however a significant difference at the 1% level in the dosage to body weight ratio at which the above control had been achieved. For B.D. this was $16 \pm 3\text{mg/kg}$ and for O.D. $12 \pm 3\text{mg/kg}$. These results can be seen in Tables 5.3 and 5.4.

Kendall's Coefficient of Concordance was then carried out on the drug data for 90 minute epochs, similar to the baseline data. Results are plotted in Figure 5.3 (Table 5.5). The analysis showed no significant agreement between subjects for either regime (Table 5.1b).

The effect of dosage regime on the pattern of occurrence of spiking

Having obtained the above data it was possible to compare the effect of a once versus a twice daily regime on the pattern of occurrence of spiking. A two way analysis of variance (ANOVA) was therefore carried out on the summed 90 minute epochs of normalised data using the R.M.L. 380Z microcomputer. Results of the ANOVA can be seen in Table 5.6. Results showed no significant difference between the two groups in the overall amount of spiking. There was however, a significant interaction between time of day and the amount of spiking occurring in each group. From

TABLE 5.3

PERCENTAGE REDUCTION OF SPIKE AND WAVE ACTIVITY
USED FOR O.D AND B.D COMPARISONS

	<u>B.D</u>	<u>O.D</u>
	50.27	62.97
	61.86	69.78
	63.17	71.32
	73.4	81.86
	89.65	93.72
\bar{x} =	67.67	75.93
S.D =	14.77	12.03

Mann Whitney U = 8 probability = .074 (not significant)

TABLE 5.4

DOSAGE TO BODYWEIGHT RATIOS OF SODIUM VALPROATE
USED FOR O.D AND B.D COMPARISONS

	<u>B.D</u>	<u>O.D</u>
	13.38	8.48
	13.48	10.9
	16.95	11.3
	18.75	11.59
	19.61	17.14
\bar{x} =	16.43	11.88
S.D =	2.91	3.19

probability = .009 (significant)

FIGURE 5.3 MEAN NUMBER OF SPIKES (NORMALISED) PER 90 MINUTE EPOCH FOR OD AND BD SUBJECTS SEPARATELY AT POINT OF 50% OR MORE CONTROL.

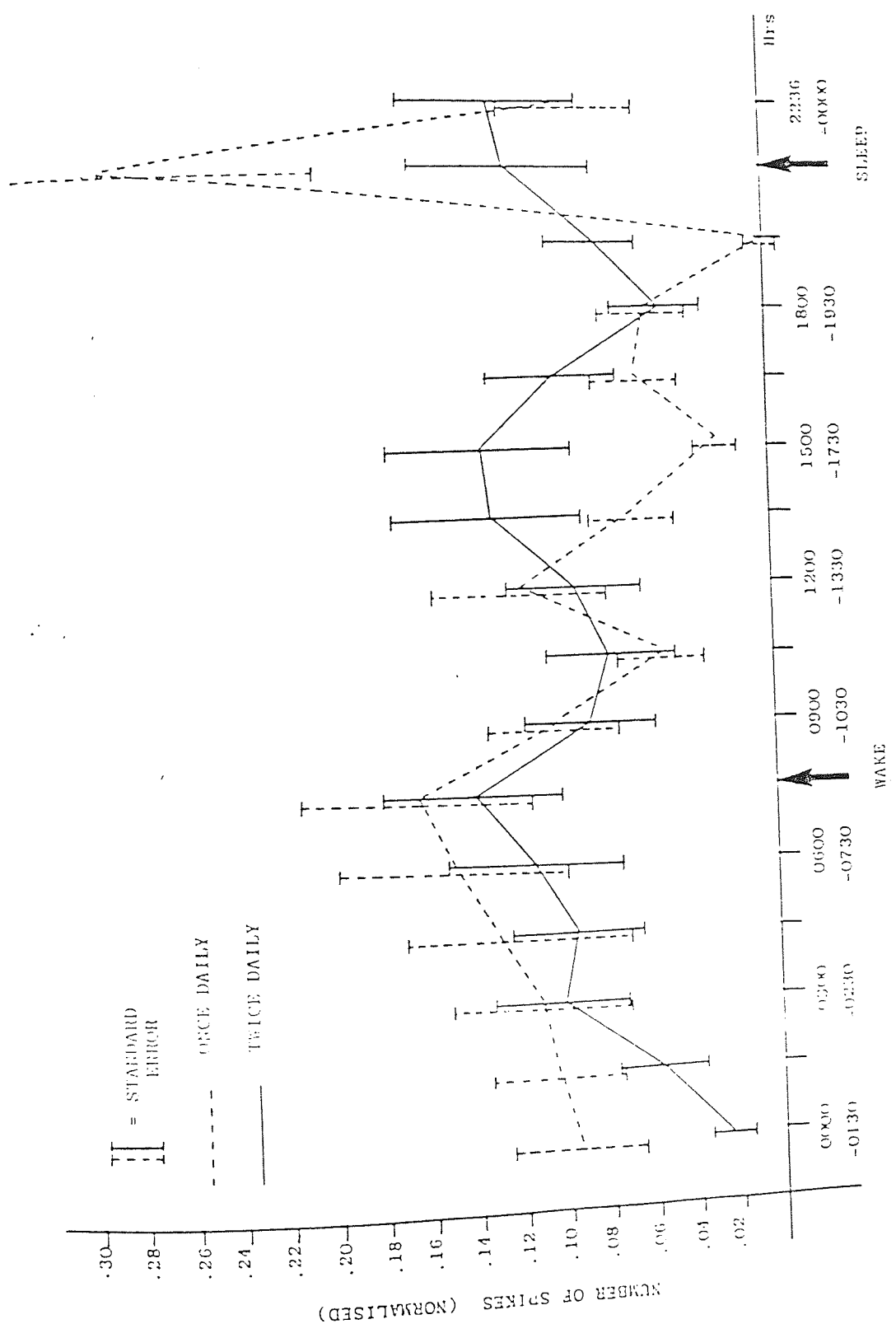


TABLE 5.5

VALUES OF EACH O.D VERSUS B.D. 90 MINUTEDRUG EPOCH PLOTTED IN FIGURE 5.3

	<u>B.D</u>		<u>O.D</u>	
	<u>MEAN</u>	<u>S.D</u>	<u>MEAN</u>	<u>S.D</u>
0000-0130	.03	.03	.09	.08
0130-0300	.06	.02	.11	.06
0300-0430	.10	.13	.11	.10
0430-0600	.09	.08	.13	.04
0600-0730	.11	.09	.15	.12
0730-0900	.14	.13	.16	.13
0900-1030	.09	.09	.1	.14
1030-1200	.08	.06	.05	.07
1200-1330	.09	.08	.11	.11
1330-1500	.13	.12	.06	.08
1500-1630	.13	.11	.03	.04
1630-1800	.09	.03	.07	.08
1800-1930	.05	.07	.05	.05
1930-2100	.08	.07	.007	.01
2100-2230	.12	.14	.29	.15
2230-0000	.13	.14	.09	.08

TABLE 5.6

RESULTS OF ANOVA FOR COMPARISON BETWEEN OD AND BD
GROUPS USING SUMMED 90 MINUTE EPOCHS
OF NORMALISED DATA

<u>Interaction</u>	<u>Variance ratios</u>	<u>Degrees of freedom</u>	<u>Significance</u>
Between groups and overall amount of spiking	0.07	1, 8	-
Between time and group	2.13	15, 120	0.05 (F critical = 1.72)
Between times of day and amount of spiking	1.36	15, 120	-

Figure 5.3 it would appear that during sleep there was less spiking in the B.D. group and during waking there was more spiking although the overall pattern of occurrence was similar for both groups.

A related t test was therefore carried out on the mean values for each 90 minute epoch of waking and sleep separately. (This was carried out in light of earlier findings that a 24 hour value might prove significant merely on the basis of change due to the sleep/wake cycle). Results showed that for waking there was a significant difference at the 5% level ($t = 1.98$, $df = 14$) but for sleep this was present at only the 10% level ($t = 1.69$, $df = 14$). This finding is somewhat curious as it appears from the graph that the difference in spiking level is more consistently higher for the O.D. group in sleep, whereas in waking there is some variation. The waking data however showed a higher significance value due to the use of the t test which measures the degree of difference between the means and not necessarily the consistency. It is unfortunate that a more appropriate test could not be found.

In order to ensure that the findings of the ANOVA were not simply due to a sampling error a similar ANOVA was carried out on the baseline data comparing subjects later assigned to the different regimes. Results are shown in Table 5.7. No significant interactions were found suggesting that the previous findings were more likely to

TABLE 5.7

RESULTS OF ANOVA FOR COMPARISON BETWEEN OD & BD
GROUPS USING SUMMED 90 MINUTE EPOCHS OF BASELINE

DATA PRIOR TO TREATMENT

Interaction	Variance ratio	Degrees of freedom	Significance
Between groups and overall amount of spiking	0.78	1, 8	-
Between time and group	1.4	15, 20	-
Between times of day and amount of spiking	0.5	15, 20	-

Analysis of ultradian rhythmicities in the occurrence
of spiking

In order to detect any rhythmicity in the occurrence of discharges, the intervals between peaks of spike occurrence were examined for each subject during waking independently, and during sleep independently. This involved counting the number of 15 minute epochs between each peak value of spike occurrence from the raw data. In order to prevent intervals containing sleep onset and waking from introducing a confounding variable into the analysis, intervals containing such a transition were excluded.

A Kolmogorov-Smirnoff test (Siegel 1956) was carried out on the resulting interval data. This test involved comparing the actual data to a theoretical distribution, which in this instance was a Poisson process. If results did not differ significantly from a Poisson process then it could be assumed that the distribution of lengths of intervals was random and that no particular time interval predominated.

As the epoch length was 15 minutes the shortest possible interval was 30 minutes. This however, caused a problem with the comparison with the Poisson distribution because in such a distribution the first value should be one.

It was therefore necessary to create a theoretical value for the first value for one 15 minute epoch. Since there

TABLE 5.8

RESULTS OF THE KOLMOGOROV-SMIRNOFF TEST
IN INDIVIDUAL SUBJECTS FOR WAKING AND SLEEP INTERVALS

	<u>Waking D Value</u>	<u>n</u>	<u>Sleep D Value</u>	<u>n</u>
M.M.	.20	11	.14	9
S.B.	.06	13	.14	10
M.N.	.35	8	.15	7
J.P.	.16	18	.14	10
R.M.	.21	9	.14	8
K.S.	.12	13	.15	6
J.O.	.11	14	.10	8
L.B.	.13	15	.10	10
E.C.	.09	16	.15	11
L.F.	.31	11	.14	11

was no reason other than the limitation of the analysis, that 15 minute epochs could not be present, this was felt to be legitimate and the value was determined in the following manner.

The mean value for the Poisson distribution was taken as the mean of the actual distribution with the first value missing. Once this was known the first value of the Poisson was then substituted into the actual data and a new mean value was obtained. This value was then taken as a new mean for the theoretical Poisson distribution and another first value was obtained and substituted into the actual data. This whole process was repeated until the successive values were very similar. The final first values for both the actual and the Poisson distribution had thus been obtained by interation..

The Kolmogorov-Smirnoff test showed that none of the interval data differed significantly from a Poisson distribution. Results for each subject during waking and sleep independently can be seen in Table 5.8. The pooled data for waking and sleep has also been plotted in a histogram in Figure 5.4 in order to give an overall impression.

The diagram shows a slight variation between the two conditions. However, the means of the two distributions were actually very similar (waking = 3.9, sleep = 3.8) and a Wilcoxon matched pairs signed - ranks test (Siegel 1956) showed again that there was no significant difference between waking and sleep ($t = 51$).

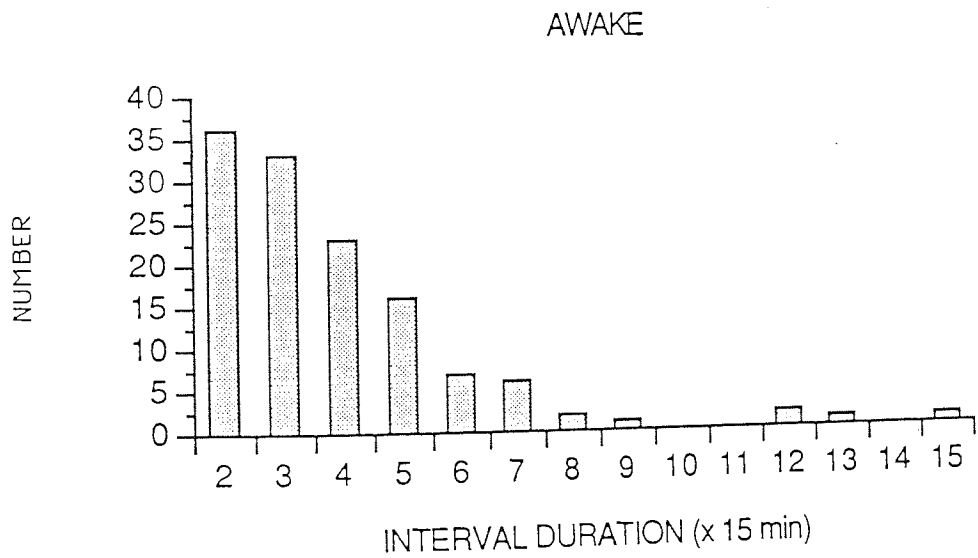
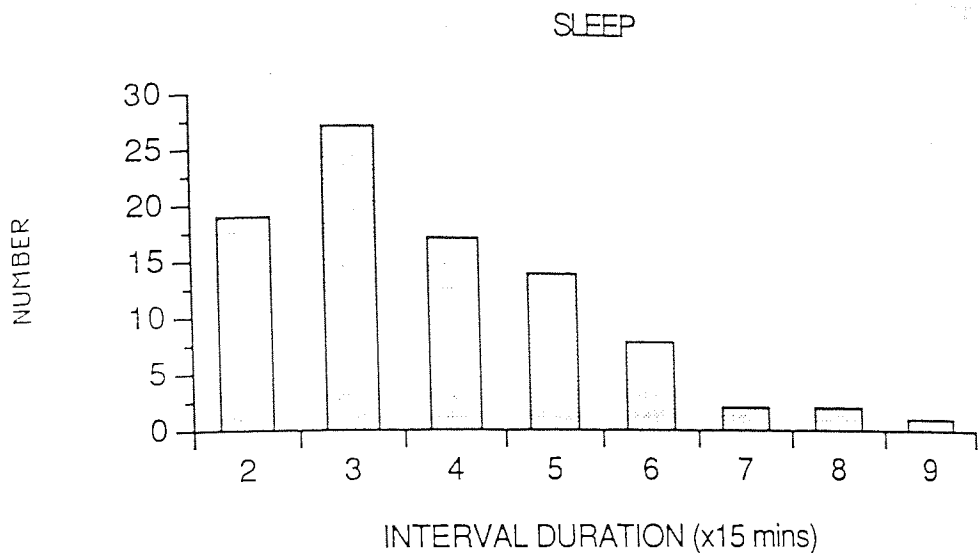


FIGURE 5.4
 HISTOGRAMS SHOWING THE FREQUENCY OF EACH
 INTERVAL LENGTH FOR ALL SUBJECTS IN WAKING
 AND SLEEP INDEPENDENTLY

There was much inter-subject variation in the pattern of occurrence of spiking during waking. During sleep however, agreement was present, with subjects showing an initial increase in discharges at sleep onset, followed by a decline until around 03.00 hours and then a further gradual rise again until waking. This overall pattern during sleep is consistent with the findings of Kellaway et al. (1980) and Martins Da Silva et al. (1984).

Similarly, as observed by the latter authors, it was found that the sleep/wake cycle produced a false agreement between subjects when the 24 hour period was examined in its entirety.

On the basis of these results it is very tempting to assume that the apparent lack of agreement between subjects during waking was due to the effect of random physiological and environmental factors. If however, an endogenous circadian rhythm did exist, one could hypothesise that its effects would still be apparent, as the random nature of external events would average out across subjects leaving an underlying process in evidence. Unlike Kellaway et al's. theory, these results do not suggest that insufficient abnormality existed during waking to produce any consistent pattern. One possible way of resolving this problem would be to completely standardise daily activities. Efforts by Martins Da Silva et al. (1984) to

do this however, proved unsuccessful. The question therefore remains unanswered.

When agreement between treated subjects on the pattern of occurrence of spiking was examined no consistencies were in evidence. The initial conclusion would therefore be similar to that of Kellaway et al. (1980), ie. that treatment randomises the pattern of occurrence of spiking. However, the results of the ANOVA would suggest that the lack of concordance between subjects would have, at least in part, been due to the effects of different dosage regimes producing a different, and sometimes opposing, pattern of occurrence of spiking. If the baseline and drug graphs are compared it would appear that during sleep, the overall pattern is preserved despite treatment. The waking data however, again shows considerable variation.

Comparison of the two drug regimes implies that during sleep the overall level of spiking is greater on a single nightly dose. During waking however, although less consistently so, spiking was more abundant in the B.D. group. These findings are almost impossible to explain on the basis of serum level findings. It is perhaps conceivable that the 9 hour delay between the evening dose and the peak serum level found by Cenraud et al. (1981) could explain the lower incidence of spiking in the B.D. group in the early hours of the morning. However, it is impossible to explain the fall in the level of spiking in the early evening in patients on O.D., in terms of any

serum level model since this was the time at which Stefan et al. (1984) found the lowest serum levels of the day. Neither is it possible to accommodate these findings by employing any theories of a delay between peak serum level and drug effect.

The only sound conclusions which can be drawn from this data are, firstly, a pattern exists during sleep which is not over-ridden by medication whether given in a single or a divided dose. Secondly, an O.D. regime does not cause any exacerbation of discharges at any particular time of the day due to falling serum levels. Why the two regimes appear to differentially affect waking and sleep remains a matter for further research. An interesting finding was also that although the percentage reduction in spike and wave between the two groups did not differ significantly, the O.D. group had a lower dosage to body weight ratio suggesting that an O.D. regime was more effective at least at this stage in the study, ie. at 50% or more control.

Analysis of the intervals between peaks of spike occurrence suggest that the length of interval is randomly determined as the distributions did not differ significantly from a Poisson process. It is very tempting to assume (as have other authors) that because most intervals fell between 30 minutes and 135 minutes periodicity was present. These findings are however, an artefact produced by the chosen epoch length and not a genuine periodicity. As suggested by the lack of a significant difference from a Poisson process, given sufficient epochs longer intervals

would have been present. Similarly, with short epoch lengths additional briefer intervals could have emerged. This data does not therefore suggest any overall ultradian rhythms during waking or sleep.

It is still possible however, that a certain length of interval was predominant at a certain time of day although this does not appear to be related to waking or sleep as the Poisson distribution for the two conditions did not differ. Although other authors state that such "modulated Poisson processes" were found, little or no details were given.

In general therefore, this study has shown that even in a very homogenous group of patients there are considerable inter-subject variations. Any agreement which was present was seen consistently during sleep, nor was this affected by sodium valproate itself or the regime in which it was given. In view of the inconsistencies during waking which cannot be explained by the evocation of random variables, it would seem highly likely that it is the sleep cycle itself which imposes any rhythmicity which was found. An endogenous circadian cycle is therefore an inappropriate model.

The study produced no evidence to suggest that once daily administration of sodium valproate was any less effective than twice daily due to the effect of possible fluctuating serum levels on spike occurrence. Nor was there any evidence for ultradian periodicities in the occurrence

CHAPTER 6

GENERAL CONCLUSIONS

GENERAL CONCLUSIONS

The misconceptions of Galen and his contemporaries are easily understood in light of certain aspects of epilepsy which have been discussed and investigated in this thesis. It has been shown that there are several factors which make epilepsy difficult to diagnose and can confound attempts to evaluate treatment in a controlled manner.

Firstly, there may be nothing to distinguish the epilepsy sufferer between attacks, from a member of the normal population. In a quarter of sufferers in the present study, the basic EEG was normal and in an equal number it showed changes which may be present in the basic EEG of ~~people without epilepsy~~:

Secondly, the symptoms of epileptic attacks are extremely diverse and can appear very similar to other types of episodic disturbances. An analysis of ictal components of attacks suggested that injury and incontinence can occur in both epileptic and non-epileptic attacks and there were few, if any, distinguishing features which were singly diagnostic. The recording of the EEG during attacks in these patients is therefore an invaluable addition to the clinical history. This makes the work of early investigators such as Gowers and Jackson, who did not have the advantage of the EEG, even more to be appreciated.

The fact that there is no totally conclusive diagnostic test makes epilepsy an ideal "peg, as it were, upon which the hysterical hat is hung" (Dreifuss et al.(1981) quoting Sigmund Freud). Thus patients with psychological disturbances add to the problems of diagnosis by producing attacks which mimic genuine seizures.

The final problem which makes diagnosis and treatment difficult is the fact that the time of occurrence of attacks is unpredictable in most patients and so a long EEG sampling time is required. Furthermore, in some patients with absence seizures, attacks may go unnoticed and so the effect of treatment can be difficult to assess.

How then, can ambulatory monitoring help to solve some of these problems?

Firstly, it enables a large group of patients, whose epilepsy is not severe enough to warrant admission to special epilepsy centres, to be investigated in greater depth. Once the apparatus is in position it will function for several days with a minimum of attention from the patient or the EEG technician, hospital admission is therefore not required. The alternative method is radio or cable telemetry which is expensive in terms of time and resources and places the patient in an artificial environment during which the normal pattern of attacks may not be found. It must be stressed however,

that for patients requiring surgery, ambulatory monitoring is not a substitute for investigations such as multichannel telemetry, video recording and depth recording techniques.

As well as providing scope to investigate a larger group of patients, ambulatory recording is more acceptable to the patient himself. Children in particular, may find hospital admission distressing and it is unfortunate that many adults with epilepsy find themselves admitted to psychiatric wards for assessment.

If a service is to be provided for such a large group of patients, the technique must be compatible with the normal running of an ordinary EEG department. There is no doubt that to the uninitiated, recorder application and the replaying of tapes can be very time-consuming. The following measures however, can help a service to run smoothly and enable the benefits to outweigh the costs.

Firstly, the appropriate patients must be chosen, ie, those whose attacks are sufficiently frequent to occur during the recording period. Secondly, there must be the possibility of prolonging the recording if attacks do not occur during the first day or if recorded attacks are unclear. It is often advisable to warn the patients beforehand that this may happen so that they can make appropriate arrangements. Thirdly, a

artefacts which are likely to

be encountered with normal ambulant subjects should be acquired, and all subsequent patients should be given a diary sheet on which to log their daily activities. Fourthly, detailed descriptions of attacks should be obtained from observers or, if possible, from the patient himself. This gives the reviewer a better idea of artefacts which are encountered during the attack and also an idea about the possible interpretation to be placed on the EEG findings.

Finally, prior to the ambulatory recording a basic EEG should be performed. This is especially important if a 4 channel recorder is used as it gives the reviewer a more extensive view of the background EEG activity and can guide the positioning of electrodes. If no abnormality is found then electrodes which include areas most likely to record abnormality but less likely to produce artifacts should be chosen. The anterior temporal regions are most likely to show abnormality in adults but are also likely to produce muscle from the jaw and eye movement. As shown in the present study, slightly higher temporal channels which do not extend as far forward as F7 and F8 will adequately record both generalised and partial seizures.

If these measures are followed the only prohibitive factor to an ordinary EEG department may be the initial cost of the equipment (especially the 8 channel recorder) and also the running costs. One way of reducing cost is to use tapes six times and to

perhaps consider the use of tin electrodes. The present study has shown that ultimately the benefits to the patient and the consultant outweigh the cost. Ambulatory monitoring was useful in over 50% of the patients investigated and provide around ten times as much information as a single basic EEG.

In the patients in whom attacks were recorded, 22% of adults showed positive evidence for epilepsy whereas in children positive evidence was found in 50%. A preliminary follow-up of patients with negative EEG findings during attacks, showed that the results of ambulatory monitoring were consistent with the final diagnosis in 67% of patients. Most of these were being treated unnecessarily with anticonvulsants which were subsequently withdrawn.

Thus ambulatory monitoring helped to differentiate patients with epilepsy from non-epilepsy sufferers by prolonging EEG sampling and allowing attacks to be recorded. It also helped to ensure that only patients with epilepsy were being treated with anticonvulsant medication.

The unpredictable manner of occurrence of epileptic attacks was illustrated by the study of circadian rhythms of absence seizures. There was little agreement between subjects on the time of occurrence of discharges during waking, but during sleep there was more agreement. It was thought to be related

to the sleep/wake cycle and was not an endogenous rhythm related to seizure production. Although other authors have demonstrated briefer periodicities of up to 2 hours, there was no evidence for these in the present study. Ambulatory monitoring had therefore thrown little light on the possible mechanisms of seizure production.

It did however, show that a single basic EEG failed to reveal discharges of spike and wave activity in 20% of treated patients who did show abnormality during a 24 hour recording. It was also of value in clarifying the number of attacks which patients with absence seizures were experiencing. On average only about 11% of actual discharges were noticed.

Repeat recordings in one patient showed a gradual reduction in discharges as medication was increased. Previously this subject had not complied with his medication because his own perception of the benefits was limited. Knowledge of the ambulatory EEG results gave him the confidence he needed to comply with his medication.

Thus ambulatory monitoring can help to assess the effect of medication for both the doctor and the patient. This was further illustrated by the investigation into once versus twice daily administration of sodium valproate.

sodium valproate is

the drug of choice because it has few side effects and does not impair learning. A study of 20 patients showed that it was a highly effective drug with only one patient requiring alternative medication. Results also showed that sodium valproate was equally as effective whether given as a single dose at night or as a divided dose.

The study of the temporal distribution of discharges in patients on partially effective treatment corroborated this finding. There were no sudden increases in abnormality at any particular time of day in patients on an OD regime, as might have been expected with fluctuating serum levels.

The two studies combined therefore, have shown that once daily sodium valproate is equally as effective as twice daily. A once daily dose would obviously help those patients and parents who find compliance difficult.

As well as assessing the effect of therapy, ambulatory monitoring ensured that the minimum amount of drug necessary was given to each patient. Three patients were controlled at less than 15 mg/kg and the mean dose for all subjects was 22 mg/kg with an average reduction in discharges of 99%. Furthermore minimising the dosage ^{may} have reduced the incidence of side effects.

It has been shown therefore, that ambulatory monitoring regime in patients

who have absence seizures. It is also valuable as a method of assessing the effect of the environment on attacks. Ambulatory monitoring is the only method which allows patients to be recorded in their normal environment. Children with educational difficulties for example, can be monitored at school in order to determine whether sub-clinical discharges account for poor school performance.

In summary, this work has shown that ambulatory monitoring is a valuable addition to the clinical history and the basic EEG in patients with epilepsy and related disorders for the following reasons.

- a) It enables a large group of patients, whose epilepsy is not severe enough to warrant admission to special epilepsy centres, to be investigated in greater depth.
- b) By increasing EEG sampling time it allows symptoms to be recorded which can help to differentiate between epileptic and non-epileptic attacks.
- c) It can also help to clarify the seizure type so that the appropriate medication can be chosen.

- d) It is the only method which allows patients to be monitored in their normal environment so that the pattern of occurrence of attacks can be investigated and the effects of treatment assessed.
- e) It provides an alternative to laboratory sleep recording in patients in whom the basic EEG is equivocal or who experience their attacks in sleep.
- f) The information provided by the ambulatory EEG during attacks, is more extensive and more accurate than the information provided by a single basic EEG.
- g) With careful planning, selection of appropriate patients and a high technical standard it can be used routinely in any EEG department.
- h) It can give greater confidence to the diagnosis and prevent certain patients from being treated unnecessarily with anticonvulsants.

Suggestions for further research

In the study described, 8 patients were referred for
and in the 4 who

experienced attacks, results were useful. The number of patients referred for this reason in recent months has steadily increased and it appears that 8 channel ambulatory monitoring is a useful way of differentiating between generalised and partial seizures. If more extensive information is required it is possible to apply two 8 channel recorders to the same patient. If one channel from each recorder is placed close to the other, it is possible to synchronise the print-out (this method was used for comparison of on head and off head preamplifiers). Thus a print-out of 16 EEG channels during attacks can be obtained. Although it would require additional timing devices and two playback units, the 16 channels of information could be used in conjunction with the new generation of recorders which convert the EEG into a coloured topographical display.

Another recent trend is for most patients to be recorded on 8 channels. It has been shown that 8 channels provide better topographical detail and enable easier differentiation of genuine abnormality from artefact. Thus, only patients with absence seizures are now recorded on 3 channels, because abnormality is generalised it is easily discerned. This also saves time for staff and patients who undergo repeated investigations for assessing the effect of therapy.

The more accurate timing of the 8 channel recorder also
with video recording.

So far, patients with very frequent attacks have been recorded in hospital and the video has been synchronised with the EEG by displaying a clock on the film.

As well as providing valuable clinical information this can help with the interpretation of artefacts. Eventually it may be possible to video record patients who have attacks during sleep, at home.

The value of the all night sleep EEG is an area which requires further investigation and this may be more feasible when a larger number of 8 channel recordings have been carried out.

The significance of inter-ictal abnormalities in the background record also requires further investigation. The incidence of EEG abnormality in a 24 hour period, in normal subjects especially children, is as yet undocumented and is an area for further research. Unfortunately the pressure of clinical referrals does not allow for this.

Other authors have noted that interpretations placed on inter-ictal EEG abnormalities can vary from reviewer to reviewer. It is therefore important to assess the reliability of interpretations placed on the EEG during attacks using reviewers from different laboratories. The possibility of carrying out such a study is at present being explored.

In conclusion, ambulatory EEG monitoring has been carried out routinely in our own department since 1981, initially using a 4 channel recorder and later an 8 channel. In the first year 53 investigations were performed, this figure has grown steadily with 126 investigations being carried out last year and a projected figure of 200 this year. This thesis has reviewed the findings of the first 250 investigations. As with any new technique there were early technical problems and it is hoped that the results presented have demonstrated that these are not insurmountable. The increased adoption of the technique in other EEG departments would, I have no doubt, provide a better method of diagnosis in a wider range of patients. A reduction in costs would make this even more viable for the ordinary EEG department. In our own region ambulatory monitoring has given greater confidence to the diagnosis and will continue to help the choice of treatment in patients with both epileptic and non-epileptic attacks.

APPENDICES

APPENDICES

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| Appendix | II | Recorder and replay specifications |
| Appendix | III | Description of procedure sent to patients with appointments |
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| Appendix | VI | Instructions for continuation of recordings |
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APPENDIX I

1981 Classification of Epileptic Seizures



Aston University

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APPENDIX I (continued)



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APPENDIX I (continued)

PROPOSAL FOR REVISED SEIZURE CLASSIFICATION



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APPENDIX II

Specifications of 4 channel recorder



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APPENDIX II (continued)

Specifications of 4 channel replay system



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APPENDIX II (continued)

Specifications of 8 channel recorder



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DIV III
APPENDIX II (continued)

Specifications of 8 channel replay system



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APPENDIX III

Description of procedure sent to
patients with appointments

24 HOUR EEG RECORDING

The 24 hr. EEG monitor records very small electrical signals from the brain by means of eight small silver discs which are placed on the scalp and hidden beneath the hair. Concealed leads are connected to a small tape recorder which is worn on a belt or shoulder strap. After having the apparatus connected in the department you are able to return home for the duration of the recording and only need to come back to the Unit to have the silver discs removed. The whole procedure is completely harmless and there is no reason why you cannot carry out your daily routine.

To ensure as good a quality a recording as possible we do ask that you arrive with clean hair, entirely free from grease, cream or lacquer.

APPENDIX IV

Instructions to patients

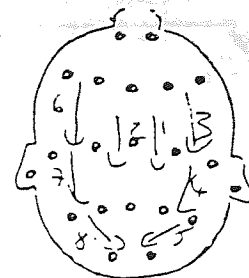
ADVICE FOR 24 HOUR EEGs

- 1) The recorder and the head attachments are rather fragile and very expensive to replace, so please try to avoid anything which might damage them e.g. bathing and any very energetic activities.
2. Please fill in the left hand side of the sheet every fifteen minutes describing briefly what you were doing.
- 3) Note in particular any interference with the electrodes e.g. hair combing, vigorous head movements (e.g. tooth brushing), wires being tugged, electrodes becoming detached.
Also note down running or other energetic activities.
- 4) If you have an attack or see the person being monitored having an attack, please do not hesitate to press the Event Button and note down on the diary sheet what happened. (The button places a marker on the tape which is only detectable on replay).
- 5) Please tape the wires lower down your back at night and place the recorder under your pillow so that the wires do not get tangled around your neck.
- 6) Finally, please note down the time that medication is taken.

APPENDIX V

Patient diary sheet

NAME _____
 RECORD NUMBER 162 17468
 DATE FRI - SAT
 START 14-00 FINISH 12.50 SAT.



TIME	ACTIVITY	REMARKS
0900	Asleep	
0915	"	
0930	"	
0945	"	
1000	"	
1015	"	
1030	Awake - Tablets = Tegroid 200mg Phenylin 100mg	
1045	Dressing	
1100	Wash, brush teeth, comb hair	
1115	Drinking	
1130	RELAXING	
1145	"	
1200	"	TABLETS - TEGROID 200mg PHENYLIN 100mg
1215	Eating	
1230	"	
1245	CHANGING Tape & Batteries	
1300	being Gelled	
1315		
1330	AT BEGINNING OF TAPE 163 and 162 GELLED ELECTRODES with tape on.	
1345		
1400	Comb Hair	
1415	Watching Tape	
1430	"	
1445	"	
1500	drinking Sarsaparilla	
1515	"	
1530	"	
1545	HEAD TABLETS Tegroid 200mg Phenylin 100mg	

APPENDIX V (continued)

		button pressed
1600	Went up stairs	
1615	Washing Tels	
1630	" "	
1645	" "	
1700	" "	
1715	" "	
1730	" "	
1745	" "	
1800	" "	
1815	^{cooking} Had Tablets - Tegretol 200 mg	
1830	cooking	
1845	Eating	
1900	Washing up	
1915	Had Tom pressed button	X
1930	was blackout 5 mins (Tom pressed button too) was mumbling	X
1945	went to sleep for about 5 mins	
2000	Com in a room. He left me with tense head. loss of memory.	
2015	Went up stairs	
2030	Washing Tels	
2045	" "	
2100	" "	
2115	" "	
2130	" "	
2145	" "	
2200	" "	
2215	" "	
2230	Eating	
2245	" "	
2300	FINISHED EATING, COMED OUT	
2315	Washing Tels	
2330	" "	

APPENDIX V (continued)

		button press
2345	01-10 1.1	
2400	~	
0015	.	
0030	.	
0045	.	
0100	.	
0115	.	
0130	1.1	
0145	^	
0200	^	
0215	^	
0230	^	
0245	^	
0300	^	
0315	^	
0330	^	
0345	^	
0400	^	
0415	^	
0430	^	
0445	^	
0500	^	
0515	^	
0530	^	
0545	^	
6000	^	
0615	^	
0630	^	
0645	^	
0700	^	
0715	^	

APPENDIX VI

Instructions for continuing recording

TO BE REPEATED AT 24 HOURLY INTERVALS

- 1 Remove recorder from case and lift lid
- 2 Turn recorder off at black switch on top of recording arm
- 3 Pull recording arm forward and carefully remove tape
- 4 Replace with new type 'A' side up
- 5 Remove old batteries and replace new ones correct way round
- 6 Jelly electrodes by poking syring in hole in tub of electrode, abrade the skin gently and inject jelly into electrode tub
- 7 Re-stick any electrodes or amplifiers which have loosened (this is unlikely)
- 8 Switch recorder back on and put back in case
- 9 Note down start time on new sheet and write day and date on cassette case

N.B. If the dots in the middle of the time on the clock do not start flashing within 2 minutes you have done something wrong

APPENDIX VII

Example of an ambulatory EEG report

24 HOUR EEG RECORDING

Recording was made transversely across central regions and bitemporally using the 8 channel recorder. Recording commenced at 14.00hrs on Friday 9th December and ended at 1400 hrs. on Monday 12th December.

On the first day no attacks were reported. Whilst the patient was travelling home by car she is said to have leaned her head on a head rest and gone to sleep. The record at this time showed a long run of theta and delta frequencies of up to 150uV localised to the left posterior temporal electrode and which had the appearance of artifact.

At 17.50 whilst she was supervising the childrens meals there was a run of 5 c.p.s. activity with a sharp component again localised to the left posterior temporal region and accompanied by muscle artifact on the right. Again this was probably artifactual.

The background EEG showed a great deal of mu activity occasionally more marked in the left central region than the right and sometimes this activity was seen in the mid temporal derivations (these were higher placed to avoid muscle activity from the jaw). The considerable amount of drug induced fast activity at around 20 c.p.s. often gave the mu rhythm a sharpish appearance.

There was no obvious abnormality during sleep although the mu activity increased in amplitude as the patient was going off to sleep.

At the beginning of the second days recording at 14.00 the patient reported a 'very mild' seizure consisting of an aura. At the time of the attack there is much artifact as the tape was being changed but some 9-10 c.p.s. high amplitude sharp activity was maximal in the right mid and posterior temporal derivations and was irregular and asynchronous, it lasted approximately 13 seconds and was followed by muscle artifact and some theta activity mainly on the right.

At 19.09 on the same day there was a 6 second run of 4-5 c.p.s. activity in the central regions, with muscle activity simultaneously in other regions. This is possibly attributable to tooth brushing.

At 10.25 the following morning the patient reported an aura followed by a 'mild' seizure. At this time she was making beds and suddenly found herself undressed and back in bed and was confused. The event button was pressed at 102514 but there was no change in the record until 102552 when some low amplitude slow activity at 2-3 c.p.s. was seen in the right temporal regions, this lasted for 4 seconds and then the trace was obscured by muscle artifact for 19 seconds. There was then a break of one second and theta activity was seen maximally on the right, but was then again partly obscured by muscle artifact for a further 9 seconds. The record then showed theta activity at 4-5 c.p.s. on the right and in central regions, maximal in the right anterior temporal derivation. This lasted for 8 seconds and then began to slow to 3-4 c.p.s. still maximal on the right, with a sharp component only on the right for 18 seconds. Generalised slow activity at 2 c.p.s. was then seen for a further 12 seconds and continued at a lower amplitude for a further 2 minutes 10 seconds when normal background activity began to re-appear.

No further attacks were reported and the third days recording was uneventful.

OPINION: The record shows clear evidence of two attacks both beginning on the right without any strong localising features, but consisting of right-sided slow activity with on at least one occasion a run of spiking associated with this slow-wave. On the second occasion, when the patient became confused, the discharge became bilateral. These findings would be entirely consistent with a clinical history of temporal lobe epilepsy

APPENDIX VIII

Raw data for patients in investigation of once v twice daily administration of sodium valproate

SUBJECT

K.S.

SUBJECT

M.Na.

DOSAGE/D	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0	0	838	9	2.7	0	93
200	5.7	760	7.7	3.1	9.3	99
600	17.14	152	6.6	1.3	81.9	23
800	22.86	21	2.1	1	97.5	10
800	22.86	0	0	0	100	0
1000	28.57	19	2.4	0.9	97.7	8
1000	28.57	0	0	0	100	0
1000BD	28.57	0	0	0	100	0
1000BD	28.57	0	0	0	100	0

DOSE/D	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0	0	808	4	1.3	0	197
500	5.4	154	5	1.3	81	33
1000	10.9	321	5	2	60.3	69
1500	16.3	183	6	1.5	77.3	33
2000	21.7	442	4	1.3	45.3	106
2500	27.2	140	5	1.1	82.7	26
3000BD	32.6	91	5	1.5	88.8	17
3500BD	38	12	2	1.5	98.6	5
3500	38	59	3	1.7	92.8	8

APPENDIX VIII(continued)

SUBJECT
L.B.

DOSAGE OD	MG/KG	TOTAL	MEAN	SD	%EDUCTION	NUMBER
0	0	373.5	3.3	0.9	0	114
0	0	520.5	3.1	0.9	0	169
200	5.8	62.5	3.7	1.2	83.3	17
400	11.6	12.5	2.1	1	96.6	6
400	11.6	130.5	2.5	1.4	65	52
600	17.4	1.5	1.5	0	99.6	1
600	17.4	1	0.5	0	99.8	2
600	17.4	0	0	0	100	0

SUBJECT
S.P.

DOSAGE OD	MG/KG	NUMBER	%REDUCTION
0	0	971	0
500	6.8	170	82.5
1000	13.6	9	99.1
1000	13.6	40	95.9
1500	20.4	12	98.8
2000	27.2	3	99.7
1500	20.4	6	99.1

APPENDIX VIII (continued)

SUBJECT
E.C.

DOSAGE	OD	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0		0	667	7.4	3.3	0	90
200		5.7	535	7.6	4.1	21.1	71
400		11.3	247	8	1.9	65.6	31
600		17	86	5.4	2.7	82.2	16
800		22.6	47	4.7	2.1	88.9	10
1000		28.3	0	0	0	100	0
1000		28.3	0	0	0	100	0

SUBJECT
M.M

DOSAGE	OD	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0		0	332	14	4	0	23
400		10.9	97	14	3	70.8	7
600		16.4	0	0	0	100	0
600		16.4	0	0	0	100	0

SUBJECT
M.N

DOSAGE	OD	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0		0	478	17.7	2.5	0	27
200		8.5	30	7.5	4.2	57.6	4
400		17	0	0	0	100	0
400		17	0	0	0	100	0

APPENDIX VIII (continued)

SUBJECT

J.G.

DOSAGEOD	MG/KG	TOTAL	MEAN	S.D.	%REDUCTI...	NUMBER
0	0	67	2.2	0.7	0	31
400	17.6	0	0	0	100	0
400	17.6	10	2.5	1.7	85.1	4
600	26.4	0	0	0	100	0
600	26.4	0	0	0	100	0
600	26.4	80	2.8	0.9	0	29
600 BD	26.4	60	2.2	0.9	10.5	27
600 BD	26.4	63	2.7	1.2	6	23
600	26.4	118	3.5	1.2	0	34
800	35.2	15	2.5	2.5	77.6	6
800	35.2	37	2.5	2.5	44.8	15

SUBJECT

S.J.

DOSAGEOD	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0	0	952	34	33.7	0	28
400	13.3	249	12.5	3.6	74	20
600	20	339	28.5	17.2	64.4	12
400BD	13.3	133	16.6	5.4	86	8
400	13.3	0	0	0	100	0

APPENDIX VIII (continued)

SUBJECT

J.T.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0	0	120	1.8	1.2	0	67
400	9.52	5.5	1.4	0.8	95.4	4
400	9.52	8.5	1.2	0.5	92.9	7
500	11.9	0	0	0	100	0
500	11.9	2	1	0	98.3	2

SUBJECT

L.E.

DOSE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0	0	926	11.6	3.9	0	80
10	19.6	341	10.3	3.1	63.2	33
15	29.4	75	9.4	2	91.9	8
20	39.2	401.5	8.9	1.7	86.6	45
20	39.2	298	11	1.6	67.8	27

SUBJECT

J.P.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0	0	742	14.3	3.5	0	52
400	13.4	369	16.8	6.2	50.3	22
600	20.1	224	18.7	6.7	69.8	12
800	26.8	0	0	0	100	0
800	26.8	5	5	0	99.3	1
800 OD	26.8	0	0	0	100	0
800 OD	26.8	0	0	0	100	0

APPENDIX VIII(continued)

SUBJECT
J.O.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0	0	385	10.7	3	0	36
400	9	379	7.6	4.2	1.6	50
600	13.5	45.5	9.3	2.4	88.2	6
800	17	0	0	0	100	0
800	17	0	0	0	100	0

SUBJECT
D.B.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTION	NUMBER
0	0	415	5	1.3	0	83
200	6.9	523	5	1.7	0	105
400	14	86	6.4	0.7	79	14
600	21	0	0	0	100	0
600	21	0	0	0	100	0

SUBJECT
C.M.

DOSAGE B.D.	MG/KG	TOTAL	MEAN	S.D.	%REDUCTI...	NUMBER
0	0	734	16	6	0	46
400	8.2	104	13	5.9	85.8	8
600	12.4	0	0	0	100	0
600	12.4	131	13.1	5	82.1	10
800	16.5	17	8.5	6.4	97.7	2
1000	18.1	42	10.5	2.4	94.3	4

APPENDIX VIII (continued)

SUBJECT
T.F.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	% REDUCTI...	NUMBER
	0	0	565	6.5	2	87
200	8.2	76	5.4	5.4	1.7	14
400	16.3	168	4.1	4.1	1.3	41
600	24.5	30.5	2.7	2.7	0.9	24
600 OD	24.5	40	1	1	0	40
800 OD	32.7	47	2.6	2.6	1.5	22

SUBJECT
R.M.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	% REDUCTI...	NUMBER
	0	0	128.5	1.4	0.5	95
400	12.5	163.5	1.4	1.4	0.6	118
600	18.8	51.5	1.2	1.2	0.6	43
800	25	6.23	1.2	1.2	0.6	7

APPENDIX VIII(continued)

SUBJECT
J.G.A.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0	0	75	2.6	0.8	0	29
0	0	6	1.5	0.6	92	3
400	16.7	1	1	0	98.7	1
400	16.7	5.5	1	0.2	92.7	5
600	25	0	0	0	100	0
600 OD	25	0	0	0	100	0
600 OD	25	1	2	0	97.3	1

SUBJECT
S.B.

DOSE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0	0	613	17	5	0	37
400	11.3	435	12	7	29	36
600	16.95	163	10.9	9.9	73.4	15
800	22.6	8	4	0	98.7	2
800	22.6	4	1	0	99.3	1
800	22.6	0	0	0	100	0

SUBJECT
P.J.

DOSAGE BD	MG/KG	TOTAL	MEAN	SD	%REDUCTI...	NUMBER
0	0	292	14.6	7.4	0	20
400	16.7	92	30	0	68.5	3
200 OD	8.3	0	0	0	100	0

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