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METHODS OF ASSESSMENT OF ANTIEPILEPTIC DRUGS

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Epilepsy is a symptom with protean manifestations and as such it is a difficult disease in which to carry out a therapeutic trial. The methods available to research workers for the assessment of new antiepileptic drugs are hampered by the fact that epilepsy is a fluctuant condition. Although it is a chronic disorder open to study using cross-over trials and within-patient comparisons, accurate assessments cannot be easily made at any one point in time. Research workers are therefore automatically placed at a time factor disadvantage and this is especially so for those searching for quick methods of evaluating new compounds. The need for a quick and reliable method of assessing a new antiepileptic drug has long been appreciated. This article will discuss the methods currently available and we will begin by considering the most commonly used method of assessment with particular reference to some of the problems involved in conducting a controlled clinical trial in epilepsy.

Assessment by seizure counting

The traditional method of assessing response to an antiepileptic drug is by demonstrating an improvement in fit frequency. Ideally this requires a double-blind, placebo-controlled cross-over study and takes several months to complete. The proper design of clinical trials involves clearly defining the objectives of the study, attention to randomisation, removal of bias from data collection, thought of statistical analysis to be used and the fulfilment of strict criteria for patient entry to and also withdrawal from the clinical trial. The fundamental principles inherent to the design of clinical trials are detailed elsewhere (Cereghino & Penry, 1972; ILAE Commission on Antiepileptic Drugs, 1973; Bulpitt, 1975; Richens, 1975).

Patient selection

Clinical trials in epilepsy are best done on in-patients where both patient and drug supervision are more reliable. In practice, such trials of long duration are only possible in institutions for residential patients. Ideally one should look at groups of patients with a single seizure type, e.g. tonic-clonic or complex partial seizures. Unfortunately this is not always possible as many patients have more than one type of fit. It is, of course, mandatory to examine individual seizure types as some fits may improve more than others. This will help in the design of future studies and may identify those groups of epileptic patients most likely to benefit from the new drug. As the method of assessment will be fit frequency it is essential that each patient's fits be clearly defined. A change in seizure severity can sometimes be as important as a change in seizure frequency. The use of demerit points in which each fit is scored according to its type and severity provides a method of comparing several treatments in a highly controlled manner (White, Plott & Norton, 1966). Gastaut's international classification is probably the most satisfactory for the purposes of defining the type of fit

Table 1 Classification of the epilepsies, modified from Marsden (1975)

1. *Generalized seizures*
   - A. Tonic-clonic seizures (grand mal)
   - B. Absence seizures (petit mal)
   - C. Myoclonic and akinetic seizures.
2. *Partial seizures (focal fits)*
   - A. With simple symptoms
     - (i) Motor seizures
     - (ii) Sensory seizures
       - (a) Somatosensory
       - (b) Visual
       - (c) Auditory
       - (d) Olfactory and gustatory
       - (e) Visceral and autonomic
   - B. With complex symptoms (complex partial seizures)
     - (a) Automatisms
     - (b) Psychic experiences (psychomotor, psychosensory)
     - (c) Emotional and mood changes
   - C. With impaired consciousness.
3. *Partial seizures secondarily generalized*
   Indicated by:
   - A. Aura preceding tonic-clonic fit.
   - B. Focal EEG discharge preceding generalized discharge.
   - C. Focal events during or prefacing a tonic-clonic fit.
   - D. Focal aftermath to tonic-clonic fit.

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(Gastaut, 1969). A simplified version of this is shown in Table 1.

During phase 2 clinical trials the subjects will usually have more severe and poorly controlled epilepsy. This is a harsh test for a new drug but any definite improvement in such patients is all the more encouraging (Richens & Ahmad, 1975). It is usual at this stage to administer the new drug as an add-on to pre-existing medication as physicians are reluctant to withdraw therapy for fear of making matters worse. The likelihood of adverse effects and drug interactions is increased by such measures. Unsatisfactory though they are, these trials form the foundation for the preliminary evaluation of new antiepileptic drugs in man. Once the new compound has shown useful results in these patients it can then be used on a wider scale in phase 3 clinical trials. Evaluation studies at this stage will include the less severe cases whose fits have not been satisfactorily controlled by established drugs and those with newly diagnosed and previously untreated epilepsy. Whether those patients already taking antiepileptic drugs should receive the new compound as sole therapy is not easy to answer although this may be possible if there is doubt about the effectiveness of established medication. It may also be justifiable to include patients with well controlled epilepsy if the new drug is likely to produce fewer adverse effects for the same degree of control. The use of the new compound as sole treatment in newly diagnosed cases presents fewer ethical objections for here there are no problems from drug withdrawal. The assessment of a new antiepileptic drug in newly diagnosed patients has been little explored. Approximately 80% of such patients respond to monotherapy using conventional medication (Shorvon, Chadwick, Galbraith & Reynolds 1978). There is here a pool of relative responders and it is surprising that no trials of new compounds have been published using this model. Indeed, there is a paucity of controlled trials of the established antiepileptic drugs in newly diagnosed patients. This is an extraordinary omission and reflects the generally poor quality of trials of drugs used in epilepsy.

Subjects who have had only a single fit could also be included in clinical trials at this stage (see below) though there are practical problems as not all patients will go on to have subsequent fits. However, in a clinic of sufficiently large size this should not be a major difficulty provided the number of such patients is small. In practice, the opportunity of studying patients presenting after a single fit is difficult and is influenced by factors not easily controlled, e.g. speed and accuracy of diagnosis, speed of referral and hospital out-patient waiting lists. Moreover, referral policy in general practice is such that patients are often not referred until they have had two or more fits and by the time they reach the out-patient clinic many are already receiving medication.

Choice of control treatment

In the clinical trial of a new antiepileptic drug there are two choices of control treatment, an identical placebo or an established antiepileptic drug. Comparing a new compound against an established drug will indicate whether it is more active, less active or equivalent in effectiveness to the established drug. This presupposes that the efficacy of the control treatment has been proved beyond doubt but this may not necessarily be the case. There is still much controversy about the relative merits of the established antiepileptic drugs in the treatment of complex partial seizures. The effect of new drugs on complex partial seizures has previously been compared against phenobarbitone and primidone at a time when the efficacy of the control treatment had not been fully evaluated in a controlled trial in this seizure type (Richens, 1976). If both new and established drugs are found to be equally effective (without comparison against placebo) the interpretation that neither drug is effective is as plausible as that both drugs are producing benefit. Comparison of a new drug against placebo at some stage is essential and if necessary this should be done as a separate study.

The use of placebo, however, can pose ethical problems. A placebo given as a control as an add-on to pre-existing medication is entirely justified but difficulties arise when considering the use of a placebo as sole therapy in patients presenting for the first time. One method might be to use placebo following the first fit and change to active treatment after the occurrence of the second fit. There are no ethical objections here as patients are not considered epileptic until after their second fit at which point the trial ends as continued treatment with placebo becomes unethical. The method of assessment might be the time interval between the institution of placebo treatment and the occurrence of the next fit compared with the time interval between fits on active treatment. It is likely that the duration and number of patients included in this type of study will both need to be large if accurate statistical conclusions are to be drawn. The justification for using a placebo as a control treatment (sole therapy) in chronic or newly diagnosed epileptic patients, i.e. those having two or more fits, is more difficult although this may be possible where subjects have relatively non-harmful seizures, e.g. absences and complex partial seizures without secondary generalisation. Patients with tonic-clonic seizures should probably receive an established antiepileptic drug as a control.

Serum level monitoring and drug dosage

It is essential that serum levels of both established antiepileptic drugs and the new compound be

monitored throughout the study as any change in fit control may occur due to drug interactions. This is especially important where subjects are already taking antiepileptic drugs in combination. In the case of sulthiame, it was a much appreciated clinical observation that this drug exerted its most beneficial effect when given in combination with other antiepileptic drugs. Much of the evidence for its antiepileptic effect came from uncontrolled add-on studies with no pharmacokinetic data (Green & Kupferberg 1972). The inhibition of phenytoin metabolism by sulthiame was only discovered subsequently (Houghton & Richens 1974 a, b). Furthermore, unless serum levels are monitored any toxic effects due to drug interaction may be erroneously attributed to the new compound (Jeavons & Clark, 1974; Richens & Ahmad, 1975).

The dose to be used in a clinical trial is usually based on data from pilot studies done on an open basis. Clinical trials involving a fixed dosage schedule do not take into account patient variables such as differing rates of absorption, metabolism and elimination. However, this type of study would be useful when comparing a new drug against placebo where the aim is to determine if the new compound has antiepileptic properties. Furthermore it is difficult to build in a dosage adjustment scheme when a placebo is included. In comparisons of new and established drugs it is better to allow dosage adjustment to suit each patient. The rules to be adopted in changing doses and the minimum interval between increments in dosage will be based on the pharmacokinetic properties of the new drug. These are necessary to allow a steady state serum level to be achieved and assessment of fit frequency should be made only after this point. The duration of each treatment period should be long enough to allow adequate assessment of fit frequency and to look for tolerance if this is suspected.

Once a steady state level in the serum has been reached following initial administration of the drug continued stability at that level is not assured. For example, a steady state level of carbamazepine has been shown to drift downwards to a lower level during chronic administration in normal volunteers due to enzyme induction (Levy, Pitlick, Troupin, Green & Neal, 1975). This partially explains why adverse reactions at the initiation of treatment tend to improve over ensuing weeks. Patients may also have a good therapeutic response initially only to find an increase in seizures subsequently which parallels the decrease in serum levels. Tolerance to the effect of antiepileptic drugs given on a long term basis may also lead to a decline in fit control (Browne & Penry, 1973). In addition, the half-life of new compounds when administered to patients receiving other antiepileptic drugs may be significantly shorter (and occasionally longer) than when the drug is administered to drug-free volunteers (Cereghino, Van Meter, Brock, Penry, Smith & White, 1973; Patel, Levy & Cutler, 1980).

Although several antiepileptic drugs are most effective when serum concentrations are maintained within the therapeutic range it does not necessarily follow that such rules will apply to all newly developed compounds. The therapeutic range of a new compound may not be known for certain during its preliminary evaluation and in later studies such estimates may not be directly related to its antiepileptic effect. In practice, maintenance of serum levels within the therapeutic range can be difficult to achieve especially if the drug has a short half-life when marked fluctuations in serum concentration can be expected. In the case of sodium valproate, a drug with a relatively short half-life, there is evidence to suggest that the antiepileptic effect is not closely related to its concentration in the serum (Jeavons, Clark & Maheshwari, 1977; Rowan, Binnie, de Beer-Pawlikowski, Goedhart, Gutter, Van Parijs, Meinardi & Meijer 1978) although some authors express a different view (Grant & Barot 1976; Gram, Flachs, Würtz-Jorgensen, Parnas & Andersen, 1979). Using photosensitivity as a model Rowan, Binnie, Warefield, Meinardi & Meijer (1979) have shown that an acute oral administration of sodium valproate has both a delayed and prolonged effect which can persist long after the drug is detectable in the serum. Indeed, some physicians recommend single daily doses of sodium valproate (Covanis & Jeavons, 1980). This does not appear to affect seizure control adversely and may improve patient compliance.

Trial design

The measures of efficacy to be examined should be clearly defined at the trial design stage. The duration of the trial will depend on factors such as frequency of seizures in the sample studied and degree of superiority of one drug over another. New compounds which are only marginally better than their counterparts will require trials of long duration to demonstrate a significant difference between treatments especially if newly diagnosed patients with relatively infrequent fits are included. Similarly, calculations of sample size should take these factors into account and numbers should be sufficient to allow for unavoidable drop-outs and non-responsiveness. Tables are available for estimating the size of samples required to achieve results at different levels of significance. It may seem banal to mention basic principles of trial design but clinical trials which are too short and contain too few numbers are extremely common (Ambroz, Chalmers, Smith, Schroeder, Frieman & Shareck, 1978). The importance of these considerations is discussed elsewhere (Altman, 1980).

In a traditional placebo controlled add-on study it

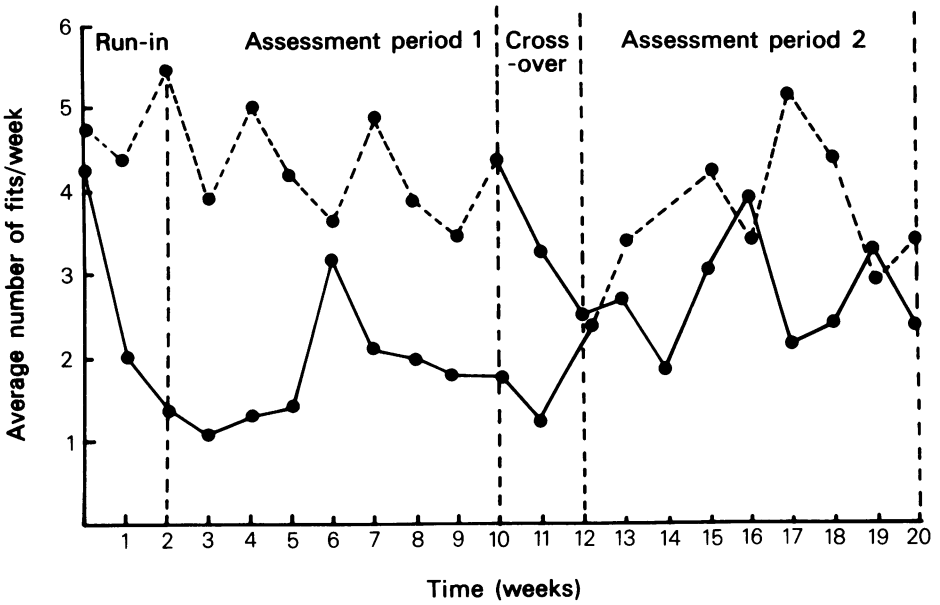

Figure 1 Double-blind cross-over trial of sodium valproate (●—●) with placebo (●···●) in 20 institutionalised patients with uncontrolled epilepsy. Following the run-in and cross-over periods which allowed gradual introduction or change of the treatment, a fixed dose of 1200 mg of sodium valproate was compared with a matching placebo. The mean frequency of tonic-clonic fits is illustrated. Analysis of variance indicated a significant difference between treatments ($P < 0.001$). (Reproduced from Richens (1976) with permission).

is usual to use a cross-over design to allow within-patient comparisons to be made. A cross-over period is desirable also so that one drug can be tailed off while gradually introducing another. This reduces the risk of precipitating status epilepticus which might otherwise occur on abrupt withdrawal of an anti-epileptic drug. It may be necessary to adjust the duration of the cross-over period to the magnitude of the risk involved. The trial should also have a run-in period so that dosage increments can be made gradually, thereby lessening the appearance of adverse effects. It may be wise to precede the actual trial with a run-in placebo period and if the patient successfully completes this period he could then enter the study (Bulpitt, 1975). Any carry-over effect of active drug into placebo period will be minimised by proper trial design. However, unexpected problems can arise especially if hitherto unknown properties of the new compound are at play. The delayed and prolonged effect of sodium valproate on photosensitivity has already been mentioned. Figure 1 illustrates the results of a double-blind placebo-controlled cross-over study showing the effects of sodium valproate on fit frequency in chronic institutionalised epileptic subjects. There is a significant improvement of fit frequency in patients taking sodium valproate. Had the authors been looking at photosensitivity and not fit frequency a cross-over or wash-out period of two weeks may have been insufficient to eliminate totally a carry-over effect and the results may then have been more difficult to interpret. Such difficulties are hardly foreseeable at the early stage of assessment of a new drug and depend on the model being examined.

Between-subjects trials offer an alternative to the traditional cross-over study. Such a trial would be useful in the comparison of a relatively new compound against an established drug, both given as sole therapy. The duration of this type of trial would depend on factors previously mentioned but it is likely to be substantially longer than the more usual cross-over trial (Shorvon *et al.*, 1978). This is a disadvantage. It also precludes the use of a placebo as control treatment. As only between-patient comparisons are possible, careful matching of patients is a *sine-qua-non* for this type of trial. The use of this design deserves consideration at some stage but it will clearly depend on the question to be answered.

When ethical considerations are of major concern and it is necessary that a trial be concluded quickly the main objective is to show that drug A is better than drug B. Sequential analysis offers a technique where results can be available rapidly and analysed at once. Following the analysis of each patient's results the decision is made whether to stop the trial or continue. Birket-Smith, Lund, Mikkelsen, Vestermark, Zander-Olsen & Hulm (1973) used this method under single-blind conditions to demonstrate the effectiveness of clonazepam in complex partial

seizures. The technique can be adapted to suit a within subjects, cross-over design using fit frequency but in other situations only between-patient comparisons are possible. This method is ideally suited for the assessment of drugs used in status epilepticus where subjects can be admitted to the trial serially. Sequential trials, however, are of little additional value when patients have to be followed for long periods and the fluctuant nature of epilepsy may impose limitations on the usefulness of this technique. Careful model selection is clearly important if sequential analysis is to be used.

Counting clinical seizures is satisfactory for dramatic events such as tonic-clonic or partial motor fits but in other situations this may not be so appropriate, e.g. nocturnal convulsions. Attempts to count clinical absences in patients with absence seizures are notoriously difficult and inaccurate as many attacks are so brief they pass unnoticed even by experienced observers. Research workers have therefore had to search for more objective methods of assessing response to medication and inevitably they turned towards the electroencephalogram.

Assessments based on changes in the EEG

Random EEG recordings

The EEG is primarily used as a diagnostic tool but many attempts have been made to correlate paroxysmal epileptiform activity in the EEG with seizure frequency. In 1935 Gibbs, Davis & Lennox introduced the theory of ictal and inter-ictal ('larval') activity and although there is still debate about the precise significance of inter-ictal paroxysmal activity the concept has persisted. The fluctuant nature of both spontaneous seizures and electroencephalographic inter-ictal activity make it difficult if not impossible to draw any conclusions from random EEG recordings. Clinical and paroxysmal EEG abnormalities occur at any time within a 24 h period but random 20 min EEG recordings sample only a small fraction of the paroxysmal activity that may occur during an entire day. Assessments of therapeutic response based on random EEGs are therefore likely to be inaccurate (Binnie, 1980).

Assessment of response to antiepileptic drugs based on random EEG recordings is compounded also by the effect of drugs on the EEG. Some drugs (carbamazepine) are reputed to cause a deterioration in the EEG whilst at the same time improving fit control. Such comments however, need to be seen in perspective. Early statements that the EEG was 'worse' during therapy with carbamazepine were based on the simplistic assumption that slow waves are somehow worse than spikes or sharp waves. Subsequent studies have given more specific information. Cereghino, Brock, Van Meter, Penry, Smith & White (1974) demonstrated that there was no reduction in paroxysmal abnormalities during therapy with carbamazepine despite an improvement in seizure frequency. This observation was confirmed by Rodin, Rim & Rennick (1974) who, in contrast, also demonstrated a fall in spike counts in subjects treated with phenytoin which seemed to parallel increasing serum levels. More recent investigations have confirmed earlier impressions. In a double-blind cross-over study Wilkus, Dodrill & Troupin (1978) compared the effects of phenytoin and carbamazepine on the EEG. Each treatment period lasted four months. There was a significant increase in both generalised slow wave activity and generalised epileptic discharges in patients taking carbamazepine. This occurred without a corresponding increase in seizure incidence. Focal epileptic abnormalities were not significantly altered however. The discrepancy between the EEG and seizure control in patients taking carbamazepine serves to underline the point that single and even repeated random 20 min EEG recordings are poor indicators in the assessment of a clinical response to antiepileptic drugs.

Inter-ictal spike frequency

There is general agreement that disappearance of inter-ictal spikes from the EEG should parallel an improvement in fit control although the evidence for this is often controversial (Bancoud, Ribet & Chagot, 1975; Carrie, 1976). Rowan, Pippenger, McGregor & French (1975) observed an increase in paroxysmal epileptiform activity in relation to various stages of sleep with suppression during REM periods. There was a marked increase in activity shortly after waking which responded to an increase in antiepileptic drug, the largest dosage being given at bedtime. The subsequent clinical and EEG improvement paralleled an increase in serum concentration throughout the night and in the morning. It is reasonable therefore to assume that disappearance of spikes is of clinical significance provided the EEG is sufficiently prolonged. Quantitation of spike frequency over several hours of EEG recording requires a system of automated analysis if its use is to become widespread. Many methods of computerised spike frequency analysis have been devised but all run into problems in differentiating true cerebral spikes from muscle activity and other artefacts. More recently Gotman has developed an automatic recognition system based on rectification of the EEG signal into half-waves and the measurement of the duration, amplitude and sharpness relative to the background. These measures are then combined to determine whether a wave is a possible spike or sharp wave. Preliminary evaluation indicates that the reliability of this method is variable but the problems are not insurmountable (Gotman,

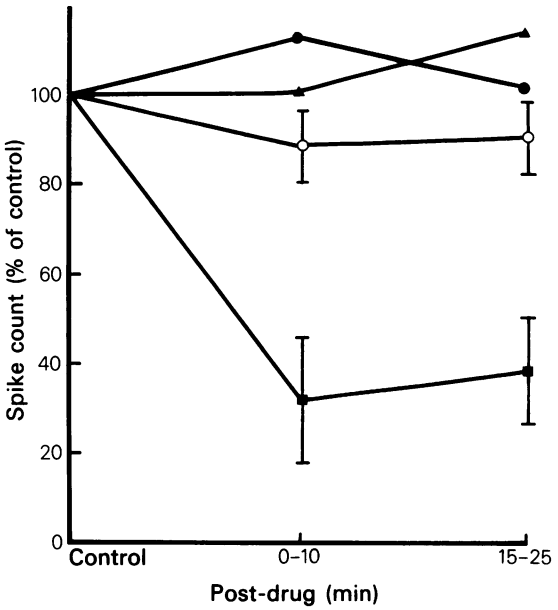

Figure 2 Results of a double-blind trial in six epileptic patients who exhibited frequent interictal spikes in their EEGs. Intravenous injections of (+)-propranolol (50 mg, ▲) (the non-β-adrenoceptor blocking isomer of propranolol) and mexiletine (100 mg, ●) were compared with diazepam (5 mg, ■) and saline (○). Assessment was by spike counting in 10 min of control EEG, and two 10-min periods following intravenous administration of the drugs. Observations after diazepam—significantly different from those after saline ($P < 0.05$). (Reproduced from Ahmad *et al.* (1977) by kind permission of the editor).

Ives & Gloor, 1979). Such a method, if reliable, would help in the study of relationships between inter-ictal spike activity and seizures, stages of sleep and level of medication. Further evaluation studies are clearly necessary and are awaited with interest.

An alternative approach to automatic spike recognition is to count the spikes by eye. Obviously this is very laborious and time consuming but the method can be adapted to suit the needs of the investigator. Ahmad, Perucca & Richens (1977) demonstrated a significant reduction in inter-ictal spike frequency following intravenous diazepam (Figure 2). This technique provides a useful and quick method for the preliminary assessment of an antiepileptic drug. The main limitations are that it can only be used in patients who have frequent inter-ictal spikes in their EEG and with drugs that penetrate rapidly into the brain. Preliminary results from more prolonged studies evaluating the effect of rectal administration of diazepam on inter-ictal spikes over a 3 h period suggests that there are marked spontaneous fluctuations in spike counts (Milligan & Richens, unpublished results). The instability of inter-ictal spike frequency complicates the assessment of drugs over prolonged periods especially those that do not have a dramatic effect. The large variance of spike frequency may make statistical analysis impossible if small numbers are studied. Drugs which have a delayed onset of action or are effective after conversion to active metabolites may therefore not be suitable for assessment using this method.

It may be possible, however, to use this technique for drugs which do not penetrate quite so rapidly into the brain as diazepam or which need to be given slowly. For example, phenytoin should be given intravenously only by slow infusion, preferably under ECG control. Assessment of inter-ictal spike frequency would need to take into account the distribution time of phenytoin which is longer than that of diazepam. In the assessment of a new drug care needs to be taken to ensure that the distribution time is not excessive otherwise a situation may be reached which is little better than random recording.

Paroxysmal spike-wave activity

Although the relationship between inter-ictal spikes and clinical epilepsy is open to question the same cannot be said of paroxysmal spike-wave (S-W) activity in absence seizures. There is abundant evidence to indicate that the frequency of absences closely parallels the amount of paroxysmal S-W activity in the EEG. In no other field of epilepsy does the relationship between EEG epileptiform activity and clinical epilepsy exist with such clarity. The EEG is potentially the most reliable tool for assessing response to medication in patients with absence seizures. This topic will therefore be considered in some detail.

An absence seizure can be defined as a brief impairment of consciousness during which the subject will interrupt his activities and then carry on as if nothing had happened (simple absence) or he may exhibit semi-purposeful movements (complex absence). During an absence seizure the EEG exhibits generalised S-W activity, classically at 3 per second. The difficulties of clinical assessment have already been mentioned. However, neuropsychological assessments made during paroxysmal epileptiform activity are often abnormal, generalised discharges producing greater abnormality than focal discharges (Wilkus & Dodrill, 1976). The generalised S-W activity during an absence seizure is virtually always accompanied by a measurable impairment of mental ability (Goode, Penry & Dreifuss 1970; Porter, Penry & Dreifuss, 1973). Browne, Penry, Porter & Dreifuss (1974) found that auditory reaction times were impaired in 57% of cases at the onset of a S-W paroxysm. This increased to 80% after a delay of

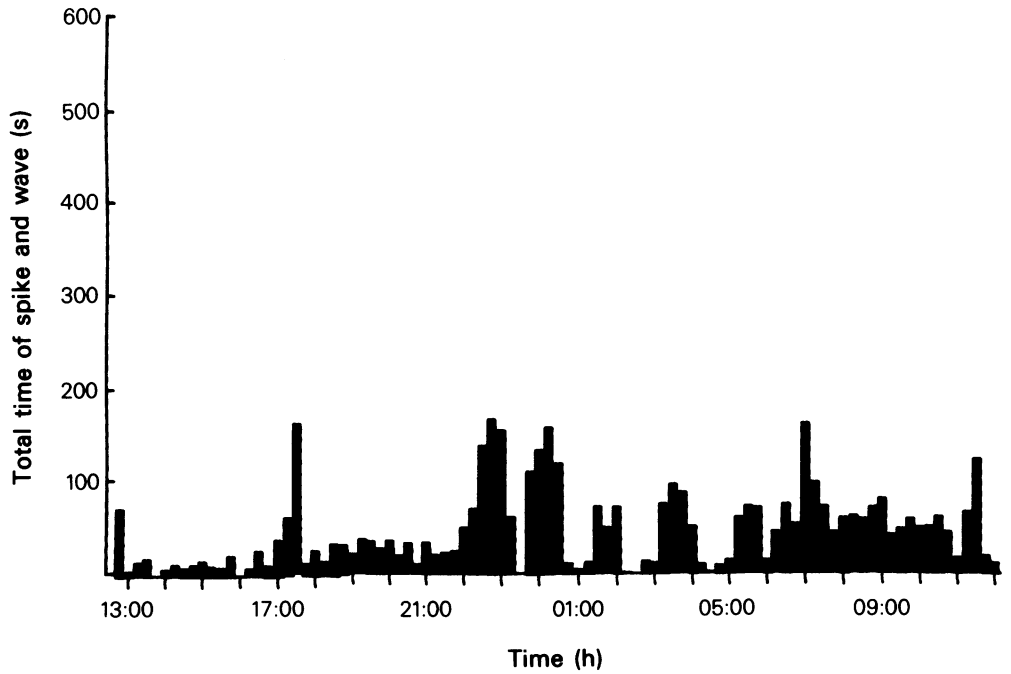

Figure 3 Computer print out showing distribution of spike-wave activity over a 24 h period beginning at 12.45 h in an epileptic patient who showed frequent paroxysms of atypical spike-wave activity in his EEG. Each bar represents the number of seconds of spike-wave activity in 15 min. Note the periodicity of spike-wave discharges during sleep (22.00–06.00 h). Each cycle lasts approximately 1.25 h. Total spike-wave = 4262 s in 24 h.

0.5 seconds into a paroxysm. Interestingly, the degree of maximal impairment of reaction time was the same in paroxysms of both long and short duration. Thus paroxysmal S-W discharges represent true ictal activity, quantification of which enables a more objective assessment of seizure occurrence to be achieved. Long periods of EEG registration are again necessary if the inaccuracies of random recordings are to be avoided. This can be achieved using radio or cable telemetry (Porter, Wolf & Penry, 1971). Serial recordings can then be done to demonstrate a reduction in S-W activity in response to medication (Penry, Porter & Dreifuss 1971). Therapy should aim at controlling all S-W discharges and not just the longer paroxysms as even shorter duration bursts can impair consciousness. Cable telemetry is to be preferred as this provides 'cleaner' recordings. The disadvantages of both systems are their expense and that the subject has to be confined within a restricted area during recordings.

More recently it has become possible to monitor the EEG in freely moving subjects (Ives & Woods, 1975). This removes the restrictions imposed by telemetry and enables recordings to be done in the home environment. A system of automatic analysis is again required if the large quantities of EEG data are to be analysed rapidly. A technique for monitoring S-W activity using ambulatory taped EEG recordings and computerised analysis has been developed at the National Hospital for Nervous Diseases, Queen Square (Quy, Willison, Fitch & Gilliatt, 1980). The EEG is recorded using head mounted pre-amplifiers and a four channel cassette recorder (Oxford Medical Systems Medilog Recorder). The EEG recordings are replayed at sixty times real time with S-W activity being quantified by an analogue detection system. Arbitrary thresholds are pre-set for both spike and wave components independently so that the occurrence of a paroxysmal discharge will result in simultaneous opening of both spike and wave gates and detection by the computer. Spike and wave detector thresholds are set according to the individual morphology of the paroxysmal discharge relative to the background and to the amount and type of artefact. Once the detector thresholds have been determined a single 24 h tape can be analysed in 20 min. Bar charts of the amount of S-W activity over 24 h are automatically plotted by microcomputer and dot matrix printer. The result is a histogram showing the amount of S-W activity in 15 min epochs over 24 h (Figure 3). This provides both a numerical and graphical representation of S-W activity over a 24 h period. The site

for electrode placement is determined from the resting EEG. Complete technical details are reported elsewhere (Quy, Fitch & Willison, 1980).

Preliminary experience indicates that the reliability of this system is variable and depends on the 'cleanness' of the recordings. The limitations of this technique are therefore similar to those encountered in automated inter-ictal spike detection *viz.* differentiation of true paroxysmal epileptiform activity from artefact. In addition, this system is useful only for those patients whose EEGs show well defined and frequent paroxysms of S-W activity on a relatively normal background. Movement artefact can be reduced using head mounted preamplifiers (Quy, 1978) but other types of artefact, particularly chewing artefact, can be more of a problem. The high amplitude electromyographic artefact from chewing can only be reduced by siting the electrodes away from the temporalis muscles. Whether or not this is feasible depends on how clearly defined the S-W paroxysms are at other sites. An alternative solution is not to use the ambulatory monitoring equipment during meals. Instead at meal times the patient can be positioned in front of a video play back unit linked to an EEG recording system. This will reduce considerably inaccuracies from chewing artefact but it will also require more expensive and sophisticated equipment and in some ways this detracts from the basic principles of ambulatory monitoring.

Reduction of S-W activity following appropriate therapy is the best indicator of a therapeutic response in patients with absence seizures. However, changes in total S-W activity over isolated 24 h periods can be misleading. Recordings done over several consecutive days in chronic institutionalised epileptic subjects with uncontrolled epilepsy indicate marked spontaneous fluctuations of S-W activity over 24 h periods (Milligan & Richens, unpublished results). Unless the drug administered is highly effective in reducing S-W paroxysms, any partial beneficial effect could well be masked by the variability of S-W activity in these subjects. As in the case of random 20 min EEG recordings, single 24 h recordings may not be sufficient to demonstrate a definitive improvement with medication. The problem of variability of S-W discharges complicates considerably the assessment of patients especially those that are relative non-responders and underlines the difficulty of drawing conclusions from studies using chronic institutionalised epileptic subjects.

It must be admitted, however, that the variability study referred to was conducted in a non-standardised environment. Ideally, drug studies in absence seizures should be conducted in a standard environment but these are difficult to design especially over long periods. Standardised structured activities are equally difficult to design and what is interesting to one patient may be boring to another. Confining subjects within a restricted area where they are allowed to do various activities (watching television, playing cards etc.) at different times and in differing sequence falls far short of the ideal standard environment. Certainly structured activities and behavioural changes do influence S-W paroxysms (Luborsky, Docherty, Todd, Knapp, Mirsky & Gottschalk, 1975; Sato, Penry & Dreifuss, 1976), but patients' interest and time spent in such activities vary from day to day as do television programmes. Whether S-W activity recorded under these conditions is representative of or significantly different from recordings done in the natural environment is unclear although any unstructured situation, characterised by boredom and lack of direction, tends to have a facilitatory effect on paroxysmal discharges.

One further problem in data analysis concerns the activity recorded during sleep. Most patients will have more epileptiform activity during the night than during the day. This consists largely of high amplitude, short duration spike and wave discharges which bear little morphological resemblance to diurnal paroxysmal activity. Such discharges are closely related to slow wave sleep with relative suppression during REM periods. Figure 3 clearly shows that nocturnal epileptic activity exhibits a cyclical pattern throughout the night. True ictal activity does not demonstrate such periodicity. Nocturnal discharges should therefore be regarded as inter-ictal. Furthermore, patients do not have absence seizures whilst asleep. It is for these reasons that the authors believe that activity recorded during sleep ought to be excluded from calculations of total S-W activity when using this system in assessing a clinical response to medication. This can easily be done by reference to the numerical computer print out which lists the number of seconds of S-W activity in each 15 minute epoch. Subtraction of nocturnal epileptic activity from the total gives the amount of diurnal S-W activity. It may not be possible to determine the exact onset of sleep from the computer print out in which case recordings or calculations should be made over a fixed number of hours of wakefulness.

Nocturnal epileptiform activity may not be entirely without value, however, in assessing response to medication. A proportion of patients with absence seizures have excessive and often prolonged fits on waking. Although the relationship of absence seizures to arousal is well recognised, the pathophysiology is quite unknown. Of the subjects who have absences on waking some show a characteristic pattern distribution of nocturnal epileptic activity with cyclical augmentation, attenuation and augmentation of S-W discharges throughout the night in relation to slow wave sleep. If the final augmentation of S-W discharges occurs just before arousal it is often continued into wakefulness and manifests itself clinically (Kellerway, Frost & Crawley, 1980).

Alteration of the time modulation of nocturnal epileptic discharges may protect those patients prone to frequent seizures on waking. It seems logical to suggest that timing of medication may be important here and perhaps the patients at risk ought to receive the bulk, if not all, of their tablets at bedtime. Although the actual amount of nocturnal epileptiform activity may not be significantly reduced by such regimes (Rowan *et al.*, 1978) it is perhaps the alteration in pattern distribution which is more important than the total number of seconds. Clinicians often prescribe medication to slot in with the fit distribution in certain individual patients. A clinical improvement is very gratifying although the reasons for this may be far from clear. Study of the time modulation of S-W discharges and its alteration by drugs may provide an explanation.

A further advantage of the ambulatory monitoring equipment is that it allows detailed study of individual patients. Using a simple trial design, a single subject prone to frequent and prolonged absences has been studied during fits. He is electively connected to the monitoring equipment whilst well and he wears it continually, though not operating, until an absence 'series' occurs. The tape recorder can then be started and treatment given, in this case either diazepam or a placebo administered rectally. An automatic recognition system is not required as for such a short study the tape can be played out on paper and the S-W paroxysms counted by eye. This increases the accuracy of the results. Preliminary observations indicate that diazepam administered rectally is highly effective in terminating an absence series as judged by disappearance of S-W activity (Milligan & Richens, unpublished results). The disadvantages of this technique are that the equipment is inoperative during the waiting period and that serial absence seizures are extremely uncommon in the general epileptic population.

Photosensitivity

Photosensitivity is defined as an abnormal electroencephalographic or clinical response to light. The relationships between photosensitivity and epilepsy have been investigated since the 1940s and stroboscopic stimulation is now widely used in routine EEG practice to uncover potential epileptiform abnormalities. Photosensitive patients are typically young females often with a family history of photosensivitiy or epilepsy. In general, the relatively young age of patients with photosensitivity may act as an obstacle to the assessement of new drugs, particularly those still under preliminary evaluation. The discovery of the Senegalese baboon *Papio papio* has provided research workers with an animal model on which to study photosensitivity. A wide variety of agents have been administered to *Papio papio* to explore the neuropharmacological mechanisms of photosensitivity. These include neurotransmitters, neurotransmitter blocking agents, neurotransmitter agonists and antagonists (Newmark & Penry, 1979). Several of these agents have been found to have a profound effect on photosensitivity although a specific biochemical abnormality has not been demonstrated. Many antiepileptic drugs have also been tested in *Papio papio* and thorough reviews are available (Killam, Matsuzaki & Killam, 1973; Meldrum, Anlezark, Balzamo, Horton & Trimble, 1975). Most antiepileptic drugs block or reduce the clinical response to photic stimulation in over 75% of animals. Phenytoin, however, is effective only in chronic doses. Most studies include mild myoclonus as a clinical measure in addition to generalised tonic-clonic convulsions. This is in contrast to the human model where responses are based essentially on specific changes in the EEG. Direct comparisons between animal and human studies are therefore difficult as different phenomena are being compared. Several authors have also noted variability in the photosensitivity of *Papio papio* which can further complicate interpretation of results. Daily, weekly and other cyclical fluctuations may appear despite standardised testing conditions (Killam, Killam & Naquet, 1967; Wada, Terao & Booker, 1972). The differing responses and variability of photosensitivity together with their expense and somewhat irascible nature makes *Papio papio* less suitable for study than the human model.

In clinical practice photosensitivity is assessed by demonstrating a photoconvulsive response (PCR) to intermittent photic stimulation (IPS). Studies show that abnormal photic responses occur in patients with a wide variety of seizure disorders. The most frequently accompanying seizure disorders in adults are of the generalised type, either generalised tonic-clonic or absence seizures. Among children the PCR is associated with a much wider variety of seizures and no seizure type predominates (Newmark & Penry, 1979). In contrast to animal studies, most antiepileptic drugs have little effect on abnormalities induced by IPS. Ethosuximide reduces the response in approximately 50% of cases. Sodium valproate is more effective, though it is often necessary to give a relatively large dose to abolish the PCR completely. In a comprehensive study, Harding, Herrick & Jeavons (1978) demonstrated complete control or significant improvement (greater than 78% reduction) of photosensitivity in 78% of subjects taking sodium valproate.

Markedly photosensitive patients are usually sensitive to light within clearly defined limits of flash frequency (sensitivity limits). The lower sensitivity limit (i.e. the lowest flash frequency which consistently evokes a PCR) is more reliable and reproducible as photic stimulators tend to produce subharmonic modulations at higher frequencies (Jeavons & Hard-

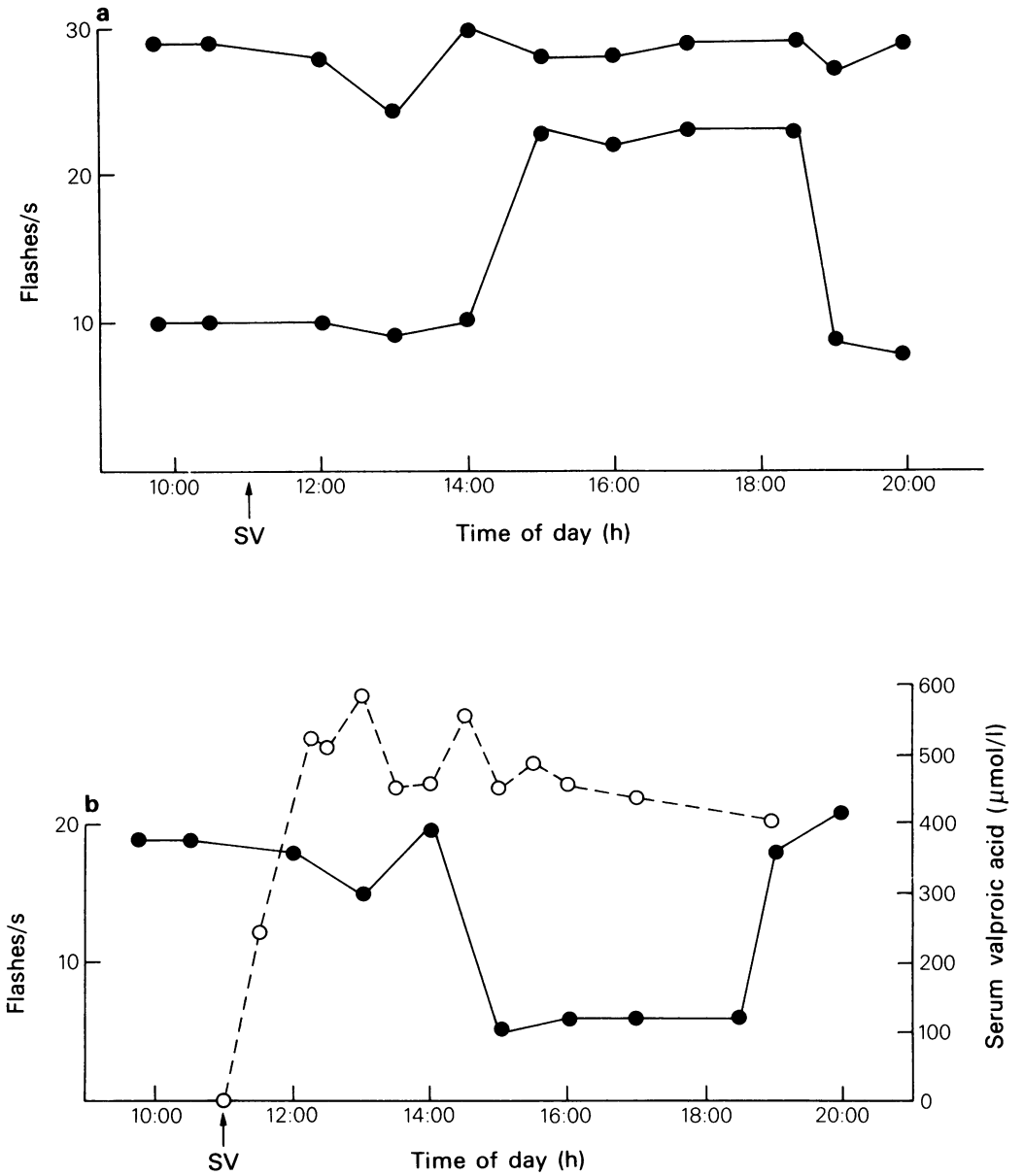

Figure 4 (a) Effect of a single oral dose of 600 mg of sodium valproate on the upper and lower limits of photosensitivity (sensitivity limits). The drug, sodium valproate (SV), was administered at 11.00 h. A photoconvulsive response was seen between the threshold limits (indicated in flashes/s). There is elevation of the lower sensitivity limit following sodium valproate administration, and the sensitivity range (i.e. the difference between the upper and lower sensitivity limits) is narrowed.
(b) Sensitivity range depicted as a single curve (●—●) with serum levels of valproic acid (○···○). Depression of the sensitivity range persists for 4.5 h but does not occur until 3 h after administration of the drug and 1 h after peak serum concentration is reached.

ing, 1975). Imperfect equipment can thus produce a falsely high upper sensitivity limit of 60 flashes/s when the actual value is 30 flashes/s. The sensitivity range, obtained by subtracting the lower from the upper sensitivity limit, can be used as a measure of photosensitivity, high values indicating more marked sensitivity than low values. Figure 4 shows the effect of a single dose of sodium valproate on the PCR of a patient with marked sensitivity to IPS. There is depression of the sensitivity range which does not begin until 3 h after administration of sodium valproate and 1 h after the peak serum concentration (Figure 4b). The effect persists for 4.5 h and in this case is due to elevation of the lower sensitivity limit (Figure 4a). Depression of the sensitivity range may be more prolonged and occasionally persists after the drug is no longer detectable in the serum. These changes are most evident in valproate naive patients but they do not disappear entirely in those on chronic therapy (Rowan *et al.*, 1979). Furthermore, improvement in the upper sensitivity limit can be maintained for 3 months after withdrawal of chronic medication (Harding *et al.*, 1978).

In studies of this kind it is vital to have a clear understanding of what constitutes a PCR. Generalised spike or polyspike and wave discharges are regarded by most as significantly abnormal responses. Bursts of bilateral high amplitude slow waves without spikes have also been considered abnormal by some (Reilley & Peters, 1973) but these are not universally accepted. Other responses to IPS such as occipital spikes and exaggerated visual evoked potentials should not be misinterpreted for a PCR. Some subjects show a diurnal variation in their sensitivity to IPS with a spontaneous reduction of the sensitivity range in the latter half of the day. It is therefore wise to precede the drug day with a control day if false positive results are to be avoided (Rowan *et al.*, 1979).

The results of photic stimulation strongly depend on the method of testing. Important variables include light intensity, flash frequency, flash duration, colour and size of visual pattern. The importance of these variables and the numerous methods of photic stimulation are reviewed elsewhere (Jeavons & Harding, 1975). Much of the published literature on photosensitivity fails to mention these variables in their methodology. Unless methodological detail is reported in published work, direct comparisons between studies will be difficult. Furthermore, the wide discrepancies between studies often reflects differing definitions of the PCR. Attention to these basic principles is of paramount importance if maximum value is to be derived from the study of photosensitivity. Whether depression of the sensitivity range by sodium valproate can act as an index of therapeutic response in differing seizure types is at present unknown although in general absences show a favourable response to this drug. The technique provides a quick method of assessing one aspect of the potential antiepileptic effect of a new drug. As the PCR is altered during sleep, being reduced during REM periods and often abolished completely during slow wave sleep (Yamamoto, Furaya, Wakamatsu & Hishikawa, 1971), this method may not be suitable for drugs with marked sedating properties.

The visual evoked response

Study of the visual evoked response (VER) aids considerably the assessment of patients with neuro-ophthalmological disorders. Many conditions affecting the visual pathways will alter the VER and this has been of particular value in demonstrating subclinical demyelinating lesions in early cases of multiple sclerosis. The latency and amplitude of individual response peaks are commonly used parameters. Analysis of the VER in clinical practice is well documented (Halliday & Mushin, 1980) but little work has been done in man on the effect of drugs on the VER.

Analysis of the VER in epilepsy has been controversial and many of the discrepancies are due to differences in technique, terminology and patient populations. The VER in epileptic patients is more variable than normals and most authors report short latencies and increased amplitude of several components. Both normal and seizure populations show marked interindividual variability of the VER, though this is more evident in seizure groups. Patients who have paroxysmal discharges in their resting EEG tend to have a more variable VER than patients who do not. There is no correlation, however, between alterations in the VER and other changes in the EEG; nor is there any typical abnormality for any one group of patients (Lücking, Creutzfeldt & Heinemann, 1970).

A possible exception are patients with photic induced seizures. This group of epileptic patients frequently have increased amplitude and/or reduced latency of several wave forms. Lee, Messenheimer, Wilkinson, Brickley & Johnson (1980) examined specifically change in the VER of photosensitive patients before and after medication and compared the differences to a normal control group. The most striking differences were changes in the morphology of the VER. Normal subjects have a very low amplitude wave immediately following the end of the stimulus. This is in contrast to untreated photosensitive patients whose responses during the immediate post stimulus period remain of high amplitude often with large slow waves. Following treatment with sodium valproate the initial peaks return to normal in configuration and latency and the late responses after the end of the stimulus are much less pronounced. The latencies to various peaks, however, are not significantly different from patients on no medication.

Such studies, interesting though they are, have little relevance to the clinical effect of an antiepileptic drug. There is no information to indicate whether alteration of the VER is indicative of an improvement in seizure control. As the VER shows marked inter-individual variation and is relatively non-specific in most epileptic groups, its usefulness as an indicator of therapeutic response would seem very limited.

Conclusions

In summary, the methods available for the assessment of antiepileptic drugs are either clinical or electroencephalographic. Each has distinct advantages and disadvantages. However, there is at present no quick and wholly reliable method for the assessment of antiepileptic drugs in man. The protracted double-blind cross-over study using fit frequency is still the foundation for the evaluation of new compounds. Other models are open to major criticisms as they are often not directly related to clinical epilepsy. Paroxysmal S-W activity in absence seizures is an exception. The foremost problem here is accuracy of rapid data analysis and the solution to this lies in the field of the scientist as it is he who will devise improved automatic recognition systems.

Photosensitivity and its influence by drugs is a relatively new area for exploration. A study of sodium valproate in patients selected on the basis of depression of their sensitivity range would be both exciting and potentially very informative. Whilst this may further identify those groups of patients likely to benefit from this drug it may also provide a useful yardstick against which new compounds could be measured.

Changes in the VER following medication indicate a cerebral effect of a drug but in view of the lack of correlation between the VER and clinical epilepsy the value of these data is unknown. As further work is likely to continue, standardisation of both terminology and methods would do much to clarify this rapidly expanding field.

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