Who could claim jurisdiction for general practitioners or what should happen in NHS trusts is not clear. The working party touched obliquely on the problem with its parenthetical suggestion that royal colleges and specialty associations might be asked to nominate screeners to cover research in private clinics. But the lack of a robust solution to the problem of fraudulent research in the NHS is disappointing: here was one instance where American style solutions had nothing to offer. Moreover, the mechanism also assumes that all parties are willing to comply—and, as many of the American cases have shown, this is often not so.

Clearly one report from one royal college is not going to solve the problem of fraud in medical research in Britain. What is important now is the recommendations on preventing fraud, and here the college is in a powerful position: its fellows are deans and professors; they chair ethics committees and sit on appointments committees. Together with colleagues in other specialties they should now start to ensure good supervision, toughen up on authorship, quiz investigators on their other work, and—perhaps most importantly—stop measuring the worth of candidates for jobs by the quantity of their research publications. To this end nominees on appointments committees should start asking for limited lists of publications. Doubts raised by the low key way that the college chose to release its report could be dispelled by its vigorous promotion of the guidelines through the conference of colleges and faculties.

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Senior assistant editor, BMJ


Regular Review

Medical assessment and treatment of chronic epilepsy

All patients should have a long term plan of treatment

Between 50 and 120 people per million population develop epilepsy each year, and about half are children. The prevalence of active epilepsy is about one in 200. It is a common misconception that most patients who develop epilepsy go on to have a chronic disease, but recent population based research has shown this not to be the case. A simple comparison of incidence and prevalence rates shows that the epilepsy ceases in most cases. Longitudinal population studies have shown that seizures remit in about two thirds of cases (remission defined as freedom from seizures for two to five years); and once a patient is in remission relapse is uncommon. The chances of entering remission are greatest in the first few years after diagnosis. If, on the other hand, the epilepsy continues without remission (for example, for five years) the chance of subsequent remission is reduced considerably.

In this review chronic epilepsy is defined as epilepsy that is still active five years or more after diagnosis. Patients with chronic epilepsy are a minority of all those who develop epilepsy, but they form a group in whom treatment may be difficult and unsatisfactory. Between 150000 and 200000 people in Britain have chronic epilepsy, of whom about one third have a seizure once or more often a month.

Patients who develop seizures may be categorised into four prognostic groups. In the first are patients with a mild, probably self limiting condition, which usually remits after a short time. This group accounts for about 30% of the total. Second are those patients whose epilepsy is easily controlled with drugs and will remit over time—another 30%. The third group comprises patients with chronic epilepsy partly responsive to drugs but with a continuing tendency to relapse (a fifth of cases); and, finally, the remaining fifth have a chronic condition in which remission is unusual and the epilepsy is largely unresponsive to normal treatment. Some factors known to influence the long term prognosis in epilepsy are shown in table I.

Patients in the first and second groups are usually easily treated with one of the standard drugs. The principles of treatment in such cases are well established and will not be discussed further. This review is concerned with the medical assessment and treatment of the third and fourth groups—patients with chronic epilepsy who require long term anticonvulsant treatment. The principles of medical treatment of such patients are different from those of treating new patients. I will describe the approach to the outpatient management of newly referred patients with chronic epilepsy based on that practised in the epilepsy clinics at the National Hospital and the Chalfont Centre. Most such patients are referred because drugs have previously failed to control their seizures, and they are usually taking combinations of antiepileptic drugs. Such patients are common attenders at neurological clinics—yet their management is often suboptimal. This review will be

<table>
<thead>
<tr>
<th>TABLE I — Factors known to influence the long term outcome of epilepsy</th>
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<tbody>
<tr>
<td>Good outcome (remission expected in &gt;70%)</td>
</tr>
<tr>
<td>Syndromes</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Seizure type</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Aetiology</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
confined to medical management, but social, domestic, and psychosocial issues may require considerable attention.

Medical assessment

DIAGNOSIS

The first step is to review critically the evidence for the diagnosis of epilepsy. As many as one fifth of patients referred to specialised epilepsy units have pseudoseizures (at least predominantly) and not true epilepsy. Such patients may have long histories of seizures with multiple admissions, intensive drug treatment, and even pseudostatus epilepticus. Often all that is needed to identify these patients is a review of previous electroencephalograms and of the circumstances and clinical form of the seizures, and a detailed witness account. Treatment should include withdrawal of antiepileptic drugs and psychotherapy.

Less commonly, diagnostic confusion arises in patients with syncope, and occasionally with other causes of altered consciousness. The converse problem may occur with some focal epilepsies, in which pseudoseizures may be misdiagnosed because of the bizarre symptoms; this is a particular problem with complex partial seizures of frontal lobe origin and with paroxysmal dystonias.

NEUROIMAGING AND AETIOLOGY

Once the epileptic nature of the seizures has been confirmed their aetiology should be identified; a thorough medical and neurological history and examination will be necessary. One common problem is detecting small structural lesions that may be amenable to surgical treatment. Computed tomography should be carried out in most patients with chronic refractory epilepsy, but it may miss small cerebral lesions. By contrast, magnetic resonance imaging has revolutionised the investigation of chronic epilepsy, and it may identify previously undetected small haematomas, areas of cerebral dysplasia, cryptic angiomas, cryptic gliomas, or focal atrophies in many patients (table II). As magnetic resonance imaging techniques improve the rate of detection of cerebral abnormalities seems likely to increase. Such structural abnormalities are important to detect, both for prognostic purposes (they worsen prognosis), and because of the potential for surgical treatment (the prognosis may improve after surgery). All patients with chronic focal epilepsy in whom surgical treatment is to be considered should have magnetic resonance imaging. Many patients with apparently idiopathic chronic epilepsy referred for re-evaluation may have an identifiable underlying cause.

CLASSIFICATION

Both the seizure type and the epilepsy should be categorised using the internationally agreed classifications. Classification is based on the clinical features, the electroencephalographic findings, and other investigations; it is important for treatment (both medical and surgical) and for prognosis.

ELECTROENCEPHALOGRAPHY

There has been some controversy about the value of electroencephalography in epilepsy—largely because of confusion about its role. Electroencephalography has great value in chronic epilepsy: it is essential to classify seizures and in presurgical evaluation, and it is also very useful in diagnosis (much more so than it is in new cases). Around 80-90% of patients with chronic epilepsy will show indubitable epileptiform electroencephalographic changes at some stage. If such changes are not seen the diagnosis of epilepsy should be re-examined. Electroencephalography has little part to play in prognosis, except in so far as it aids classification, or in the monitoring of treatment.

HISTORY OF PREVIOUS TREATMENT

The importance of taking a history of previous treatment is often forgotten, and yet this is vital in planning future changes in treatment. The doctor should attempt to document which drugs taken in the past were given a full trial of treatment and with what effect—for example, which was most efficacious, which were of least value, and which caused toxic effects? In some patients it may help to obtain previous medical records either from the general practitioner or hospital clinics. When serum concentrations of drugs have been measured the results should be recorded if possible. In this way a drug history may be constructed and related to toxicity and to control of seizures.

Medical treatment

LONG TERM TREATMENT PLAN

A long term plan of treatment should be devised for all newly referred patients. This should consist of a planned sequence of drug changes designed systematically to test the effects of individual drugs (target drugs); drugs should be added to a background regimen and given for a defined time limited trial. The sequence should be followed until a satisfactory regimen has been identified.

Construction of the plan will require decisions about the choice of target drug, the background regimen, the period for each drug trial, and the sequence of staged additions and withdrawals of drugs. A typical plan might consist of four or five target regimens and might take many months to complete. It is helpful at the onset to list the sequence of planned changes and then to try to carry through this sequence in an orderly fashion. The changes require careful monitoring—best achieved by regular visits to the same doctor in outpatients. During changeover phases the frequency of the seizures should be assessed objectively. Any tendency to overreact to short term exacerbations (which might disrupt a planned programme of change) should be resisted.

BACKGROUND DRUG REGIMENS

The background regimens should comprise the one or two drugs that the patient's history suggests have been most helpful in the past. It is seldom worth prescribing more than two antiepileptic drugs in combination: combinations of drugs neither enhance nor modify their individual effectiveness, though their toxicity may be worsened. The newly referred patient is usually taking a cocktail of drugs, which often needs adjustment before introducing a target drug trial.

CHOICE OF TARGET DRUG AND DURATION OF DRUG TRIAL

Table III shows the drugs of choice for the different seizure types, including some currently in the late stages of clinical trial. Usually, a patient's response to the introduction of

<table>
<thead>
<tr>
<th>Clinical problem</th>
<th>No of cases</th>
<th>Magnetic strength (T)</th>
<th>No (%) of patients with abnormal magnetic resonance image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe epilepsy</td>
<td>10</td>
<td>0-15</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Intractable complex partial seizures</td>
<td>35</td>
<td>0-35</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Refractory complex partial seizures</td>
<td>22</td>
<td>0-26-0-5</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Partial seizures</td>
<td>37</td>
<td>0-35</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Partial seizures 1</td>
<td>22</td>
<td>0-5</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Operated focal epilepsy</td>
<td>10</td>
<td>1-5</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Operated focal epilepsy with pathological confirmation</td>
<td>41</td>
<td>0-5</td>
<td>27 (66)</td>
</tr>
<tr>
<td>Glionea, haematomata, or ganglia</td>
<td>12</td>
<td>0-1</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Severe gliosis</td>
<td>13</td>
<td>0-1</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Mild gliosis</td>
<td>10</td>
<td>0-1</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>6</td>
<td>0-1</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Well controlled temporal lobe epilepsy</td>
<td>40</td>
<td>1-5</td>
<td>19 (49)</td>
</tr>
<tr>
<td>Intractable temporal lobe epilepsy</td>
<td>29</td>
<td>1-5</td>
<td>6 (21)</td>
</tr>
</tbody>
</table>
TABLE III—Choice of drug for adult refractory epilepsy

<table>
<thead>
<tr>
<th>Tonic-clonic or partial seizures</th>
<th>Myoclonic seizures</th>
<th>Tonic, atonic, and atypical absence seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine*</td>
<td>Clobazam§</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Phenytoin*</td>
<td>Clonazepam§</td>
<td>Barbital§</td>
</tr>
<tr>
<td>Valproate§</td>
<td>Valproic acid§</td>
<td>Carbamazepine§</td>
</tr>
<tr>
<td>Acrivastil§</td>
<td>Acetazolamide</td>
<td>Carbamazepine§</td>
</tr>
<tr>
<td>Barbirurate§</td>
<td>Nitrazepam</td>
<td>Clobazam§</td>
</tr>
<tr>
<td>Clorazapate§</td>
<td>Phenytoin</td>
<td>Phenobarbitone§</td>
</tr>
<tr>
<td>Methsuximide§</td>
<td>Piracetam§</td>
<td>Valproate§</td>
</tr>
<tr>
<td>Vigabatrin§</td>
<td>Lamotrigine§</td>
<td>Lamotrigine§</td>
</tr>
<tr>
<td>Lamotrigine§</td>
<td>Oxcarbazepine‡</td>
<td>Lamotrigine‡</td>
</tr>
<tr>
<td>Topiramate‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Drugs of choice for all tonic-clonic and partial seizures.
†Drugs of choice for primary generalised tonic-clonic seizures.
‡Drugs under phase 4 trial (not universally available).
§Drugs of first choice for myoclonic seizure.

any given drug is consistent over time; this implies that the renewed prescription of a drug previously shown to be ineffective is seldom of value, whereas (conversely) a previously useful effect is likely to be repeated. The sequence of target drugs should be based both on the drugs indicated for the type of epilepsy and on the previous drug history. This sequence should therefore consist of any first or second line drug not previously tried or any drug helpful in the past, together with new or experimental drugs if clinically indicated.

The treatment plan should specify a trial of treatment with each drug long enough to assess its effect on seizures. Necessarily this will depend on the pattern and frequency of seizures. As an arbitrary rule a drug should usually be tried for a period that would be expected to encompass three to five (or three to five clusters of) seizures, or for at least two months (whichever period is longer). (For example, if a patient has seizures monthly it may be necessary to give a drug at a therapeutic dose for five months before deciding whether it is effective.) The trial period should be with the drug at full dosage confirmed by repeated measurements of serum concentrations (if appropriate). If improvement is not satisfactory the next regimen in the treatment plan should be tried. If a target drug does produce a useful response further changes in treatment should then either aim at reducing the background drugs or at continuing the successful regimen. Usually, if introducing a target drug produces a dramatic response other background drugs can be safely reduced. Some antiepileptic drugs such as acazolamide or clobazam are given in low doses, whereas other drugs require longer periods to introduce or withdraw. The two types may be interleaved with the introduction of clobazam or acazolamide overlapping the slow withdrawal of the other drugs—and their rapid withdrawal overlapping the slow introduction of still others.

DRUG WITHDRAWAL

Individual drugs should be gradually withdrawn, one at a time. The rates of withdrawal are to some extent arbitrary; table IV shows examples of outpatient withdrawal rates. Phenytoin or valproate may be withdrawn faster if necessary—over a few days in hospital—but the withdrawal of carbamazepine or barbiturates or benzodiazepines should be carried out slowly. If a severe exacerbation of seizures occurs on the withdrawal of any individual drug re-establishing the same drug will almost always control them quickly.

DRUG ADDITION

In most clinical outpatient settings new antiepileptic drugs are best introduced in a slow stepwise fashion. This applies particularly to primidone and carbamazepine, which should both be started at a very low dose (62.5 mg and 100 mg respectively). Table IV gives the recommended weekly incremental dosages, but if urgent treatment is needed higher loading doses may be given with any of the antiepileptic drugs. The evaluation of efficacy and toxicity should not begin until a full dose is being given. Nor should a drug be withdrawn prematurely because of early side effects—these are often transient.

SERUM CONCENTRATION MONITORING

The monitoring of serum concentrations of phenytoin, carbamazepine, ethosuximide, and phenobarbitone may help in planning treatment, as changes in concentration usually correspond with changes in both efficacy and toxicity. By contrast, serum concentrations of valproate, primidone, or oxcarbazepine are not helpful as no such correlation is found. Target serum ranges are not in general useful for the other drugs (table IV).

Serum concentrations should not be measured until target dose regimens have been achieved, and there is little point in measuring serum concentrations while active drug changes are underway unless side effects are occurring. Fine tuning of dosage can be carried out once the desired anticonvulsant regimen has been reached. The optimum range is, however, only a guide to dosage. Many patients with serum concentrations outside the recommended range are receiving perfectly adequate treatment. The clinical state of a patient is much more important than the serum concentrations of drugs.

DRUG TOXICITY

All antiepileptic drugs have potential side effects, and a balance has to be made between the risks of toxicity and the potential benefits of improved seizure control. This is an individual decision. Transient side effects are often experienced at the start of treatment, and the patient should be warned about these. Treatment should not be abandoned because of such transient effects (a common mistake). If possible the target dose should be reached and the drug given a trial period before deciding about the balance between toxicity and efficacy. Patients should be counselled before starting a drug about its common or serious side effects. The use of slow release formulations of some drugs (such as carbamazepine) may reduce side effects considerably.

REFRACTORY EPILEPSY

Drug treatment has its limits, and control of seizures will not be possible in some patients with the drugs currently available (perhaps 20% of all patients developing epilepsy). If appropriate antiepileptic drugs have been given an adequate trial (as outlined above) without success the epilepsy should be deemed refractory. This is an important decision as it changes the emphasis of treatment. Medication should be simplified and reduced to minimise toxicity. If possible sedative anticonvulsants should be withdrawn. Treatment should then be stabilised, and the temptation to continue to
change (usually add) anticonvulsants in the face of continuing seizures should be resisted. The possibility of surgical treatment for the epilepsy should then also be considered.

Surgical treatment
Surgical treatment for epilepsy is considered too rarely. Several thousand people with refractory epilepsy in Britain would benefit from standard temporal lobe surgery or from other surgical procedures. The presurgical evaluation necessary to select suitable patients is complex and requires specialised procedures, and it should be carried out only in experienced units. The most common operation is the en bloc temporal lobectomy, but in recent years other procedures have been developed and at least five operative approaches are now carried out.31 32

Focal resection of epileptic tissue is possible for partial epilepsies in which the epileptic tissue is sufficiently localised to allow resection without unacceptable morbidity. Operations include the standard temporal lobectomy and the newer selective amygdalohippocampectomy, the results of which are excellent. The results of other resections (for example, of frontal cortex) are less satisfactory. A modified hemispherectomy is possible in a few patients with lateralised epilepsy of childhood onset who have a severely damaged hemisphere. The results are excellent. Several recent technical modifications to the original operation have made it safer.

 Corpus callosotomy is an operation usually reserved for severe generalised (especially secondarily generalised) tonic-clonic seizures or atomic or tonic seizures, and is palliative rather than curative.

Stereotactic operations have been tried in various forms for several decades without much success. With an increasing understanding of the underlying physiology of epilepsy, however, this surgical approach will probably gain in precision and play an important part in future surgical developments.

Multiple subpial transection is another new operation, potentially suitable for cortical epilepsy in cortical areas in which resection would be ill advised. The exact place of this operation is yet to be defined.

The main clinical problem is that of identifying those patients (a minority of all with epilepsy) who are likely to benefit. This presurgical evaluation is time consuming and arduous, and in many cases after intensive investigation surgical treatment proves not to be advisable. An evaluation should be considered only if, firstly, the seizure disorder is truly refractory to medical treatment and, secondly, the seizures are of a type or frequency that renders them so intolerable to the patient that the hazards of surgery are acceptable. This is a decision that requires a detailed knowledge of the patient and his or her epilepsy and the outcome of surgery (in terms of long term morbidity and seizure control). The successful outcome of surgery is not necessarily a matter of seizure control; it should lead to an improvement in the quality of life—and the two are not necessarily equivalent. It is not uncommon to meet patients with greatly improved seizure control in whom the psychological outcome has not been altered or has even been worsened by injudicious surgical intervention.

Medical services for epilepsy in Britain
In each NHS region there are about 20000 people with epilepsy, and almost one third of these have seizures once a month or more frequently. An average general practitioner will have about 10 patients with chronic epilepsy and perhaps two with severe refractory epilepsy. A typical NHS region has about 11 neurologists, 40 paediatricians, and seven neurosurgeons (whole time equivalents). Clearly, all patients with chronic epilepsy cannot be seen regularly by the specialised hospital services. Most patients will be treated by their general practitioners, but all should receive a neurological (or paediatric) evaluation at some point. Patients with difficult problems may be referred to neurological units specialising in epilepsy, such as those at the National and Maudsley Hospitals. There are four NHS special assessment units, which are specific inpatient units providing comprehensive epilepsy assessment: Park Hospital (for children), Chalfont Centre for Epilepsy, David Lewis Centre, and Bootham Park Hospital. Surgical treatment for epilepsy is carried out on a regular basis in only a few neurosurgical units, including Cardiff, Liverpool, Oxford, and the National and Maudsley Hospitals. Patients with mental handicap or psychiatric disorder and epilepsy should usually be referred within the local psychiatric or mental handicap services, and tertiary referral to psychiatric hospitals specialising in epilepsy (for example, the Maudsley Hospital) may also be made. Information services for patients and professional groups about epilepsy are also provided by the National Society for Epilepsy and the British Epilepsy Association. Both charities also administer nationwide networks of patient groups.

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