between centres probably imply a variability between doctors in their perception of what constitutes clinical suspicion of bony injury and the extent to which they believe an extremity radiograph might help to resolve this. If this variability could be reduced the quality of present practice would be further improved. We believe that this could be achieved by developing guidelines for selection of patients for extremity radiography similar to those already proposed for preoperative chest radiology and skull radiology.[1 5 6 9-11]

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For Debate . . .

Is there a place for placebo controlled trials of antiepileptic drugs?

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Abstract

In many patients who develop epilepsy the disease is short lived and the overall number of seizures small. The role of anticonvulsant drugs in such patients is uncertain. If treatment is merely suppressive and the disease self limiting then treatment may not be necessary in some patients. If, on the other hand, early treatment prevents the subsequent evolution to chronic epilepsy then it is imperative. To resolve this issue it is essential to undertake placebo controlled trials, in which a group of patients with newly diagnosed epilepsy is given active treatment and compared with a similar group given placebo alone.

This article is based on a paper given in May 1984 at a meeting of the British branch of the International League Against Epilepsy and on a debate held in April 1984 during a combined meeting of the neurosciences departments of the Charing Cross, Westminster, and Central Middlesex hospitals attended by members of the Association of British Neurologists.

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Introduction

For over 125 years effective antiepileptic drugs have been available. Bromides were introduced into clinical practice in 1857, phenobarbitone in 1912, and phenytoin in 1938, well before the modern idea of clinical trials was conceived. There is no doubt that these and other drugs in current use suppress seizures. This has been objectively shown in animal and laboratory work and confirmed by extensive clinical experience. As epileptic seizures can have serious social and psychological consequences and cause injury and occasionally death, withholding effective treatment to give placebo appears to have little justification. On the other hand, there is equally no doubt that antiepileptic drugs are toxic, having side effects that are potentially serious and occasionally life threatening. Notwithstanding their pharmacological efficacy the unnecessary use of these drugs is therefore unjustifiable.

In three particular clinical circumstances the need for treatment with antiepileptic drugs is uncertain: in patients with newly diagnosed disease who have had only a few seizures; in patients receiving long term treatment who are free of seizures; and in patients with continuing epilepsy that is seemingly unresponsive to treatment. Particularly important issues arise in the first group. Ethical principles that apply generally to clinical trials will apply in this case; the issues are different in studies in which placebo is added to a regimen on one or more antiepileptic drugs that patients are already taking.

The natural history of epilepsy

Questions about the role of treatment are best raised in the context of the natural history of the disease—that is, its course while untreated. Because effective drug treatment has been available for so long there is almost no statistical information on the course of

untreated epilepsy and what information there is derives from the mainly empirical opinions of early practitioners. Gowers concluded in 1881 from his large practice at the National Hospital that "the spontaneous cessation of the disease is an event too rare to be reasonably anticipated"[1]; this probably reflected most antecedent views.

What we know about the course of epilepsy is therefore based on observation of the treated condition. The traditional view that epilepsy is largely a chronic illness, with perhaps only 20% of patients achieving remission,[2] arises principally from studies of special category patients conducted in hospitals. This finding is not generally applicable to patients with newly diagnosed disease,[3-5] most of whom, as recent prospective hospital surveys have shown, achieved rapid and complete control of seizures with treatment.[4] Two lines of epidemiological evidence support this. Firstly, the lifetime incidence of epilepsy determined from cross sectional studies (the proportion of the population that has ever developed the condition) is considerably higher than the prevalence (the proportion that currently has it). Secondly, by monitoring patients from the time of diagnosis longitudinal studies from Rochester, Minnesota,[6] and Tonbridge, Kent,[7 8] clearly showed that in most patients the condition is relatively short lived and that prolonged remissions are obtained with the passage of time in an increasing number. In both studies the rate of remission was highest in the early years, roughly 70% of patients eventually entered long term remission, within 10 years of diagnosis over half had stopped taking their antiepileptic drugs, and once remission had occurred subsequent relapse was unusual.

What is the role of treatment in patients with newly diagnosed disease?

If, as these studies suggest, most patients are destined to have few attacks and short lived epilepsy treatment with drugs in many cases may not be necessary. On the other hand, because most patients receive drug treatment from the time of diagnosis it is possible that remissions are caused by treatment. If so, and if antiepileptic drugs that suppress attacks in the short term also lessen the long term propensity to recurrence, then the earlier this curative treatment is started the better—possibly after the first seizure.

Unfortunately, at the time of diagnosis in individual cases it is often not possible to predict the likelihood of seizures recurring. In the absence of an identifiable underlying cause or obvious provocation an isolated seizure is not usually considered to warrant treatment with antiepileptic drugs. Depending on the interval between seizures, treatment is usually recommended after two or more seizures have occurred, an arbitrary practice that reflects the uncertainty over the need for treatment; there may be no a priori grounds for assuming pathophysiological differences between patients who have had single attacks and those who have had more. In the only such population study of non-febrile seizures about two thirds of the patients had fewer than 10 seizures.[7 8] Most of the patients received treatment at some point, even if only for a short period, but if epilepsy were defined as a condition characterised by 10 or more seizures rather than two or more only a third of these patients would have been diagnosed as having it.

The need for placebo controlled studies

At present it is not clear whether treatment with antiepileptic drugs is indicated for all patients with newly diagnosed disease to suppress seizures or induce long term remission, or both, or for only a minority of such cases because in most cases epilepsy is self limiting and remits spontaneously. Whichever interpretation is correct, the extent to which treatment is superior to no treatment needs to be established so that some estimate can be made of how this benefit balances the risks of toxicity and the inconvenience of regular treatment with drugs. Such information can be obtained only by comparing matched series of patients with and without treatment. As in all drug trials patients treated with placebo are better controls than an untreated group as the tested drug may have placebo as well as pharmacological action.

There are problems in the design of such a study, many of them peculiar to epilepsy: what criteria for selection should be used; whether there should be upper and lower age limits; whether patients with specific aetiologies should be excluded; and whether patients who suffer certain types of seizure should be excluded—for example, primary generalised tonic-clonic seizures because of their generally good prognosis or complex partial seizures because of their poor prognosis. What should be the criteria for switching those treated with placebo to active drug treatment; at what stage should this be done, how many seizures should patients be allowed to have while being treated with placebo, and for how long should placebo be given? What number of patients and duration of follow up are needed to detect differences in long term outcome?

Although these may appear to be additional ethical considerations, they are practical difficulties only once the concept of placebo control in epilepsy is accepted and no greater than the difficulties arising in clinical trials in other medical conditions.[9] They do not in themselves detract from the argument that placebo controlled studies, as defined here, are not only ethical in epilepsy but necessary.

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Is there any specific danger to workers from the inhalation of sawdust?

The occupational hazards associated with the inhalation of sawdust may be considered as acute and non-acute. Acute illness, consequent on the absorption of various alkaloids from sawdust, takes the form of a "toxic" syndrome. This usually has a prominent neurological component, with pronounced lethargy, headache, mental dullness, and lachrymation.[1] Such syndromes are associated with exposure to rather exotic woods and are uncommon in the United Kingdom. The few cases that have been reported here were confined to workers making African boxwood shuttles, bushes, and bearings for textile machinery. Within that industry the condition is a prescribed disease. Longer periods of exposure to certain wood dusts may give rise to occupational asthma or nasal carcinoma. Occupational asthma among woodworkers is well documented, and one of the woods most thoroughly investigated is western red cedar (*Thuja plicata*).[2] In this instance, the responsible allergen is thought to be plicatic acid. Although most cases of asthma are probably caused by constituents of wood resins and gums, some such as maple bark asthma are undoubtedly due to sensitisation to fungal contaminants. Carcinoma arising from the nasal mucosa or paranasal sinuses is a prescribed disease in the woodworking (and shoe manufacturing) industry. Squamous cell and adenocarcinoma are the two main types encountered, the former being considerably more common. The latent period is usually long, extending to 40 years or more, but cases have been reported 15 years after exposure began.[3]—W R LEE, professor, and A R SCOTT, lecturer, in occupational health, Manchester.

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