

many gave "not enough energy" and "too old" as reasons for not exercising. Precautions also need publicity—for example, warming up and cooling down gradually, avoiding vigorous exercise during infections, and (for older people) having a medical check before starting vigorous activity. Doctors are in a key position. Some general practitioners have diplomas in sports medicine, and a few are setting up exercise programmes. As the Royal College of Physicians says, however, all doctors should ask about exercise when they see patients, especially during routine health checks, and advise on suitable exercise and local facilities.<sup>6</sup> Their frequent contact with women and children provides a valuable opportunity. Excluding ischaemic heart disease and also checking blood pressure before vigorous activity is started are important precautions. But above all doctors could help to create a cultural change whereby the habit of exercise becomes integral to daily life.

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## Epilepsy and stress

### *Time for proper studies of the association*

Epilepsy was once regarded as a mental illness and was classified among the neuroses. In the last century the organic component of epilepsy was more clearly recognised, and interest in its psychological component waned.<sup>1</sup> Thus epilepsy came to be attributed to a physical disorder in the brain (whether determined by genetic constitution, structural damage, or new or aberrant growth), which caused characteristic changes in neurotransmitters, leading to seizures. According to this view, epilepsy originates in the brain and is therefore a medical condition, rightly treated by neurologists or other doctors.

This, however, is too narrow a view and leads to medical care becoming a futile exercise in counting pills and seizures and maintaining prohibitions. The result: an overtreated, unhappy patient. Although epilepsy may take place in the brain, it may profoundly influence the morale, wellbeing, self image, and lifestyle of its sufferers.<sup>2</sup> Epilepsy may briefly change the way a person thinks, feels, and acts—but how someone thinks, feels, and acts may also change his or her epilepsy. Epilepsy takes place in a brain that also contains a mind, which is subject to other influences, both internal and external, and to differing states of arousal and emotion. These may have their own influences on the epilepsy.

Many people with epilepsy (if they are asked<sup>3</sup>) will tell their doctor that their emotions, states of arousal, and internal and external stresses may profoundly influence the frequency of their seizures: for some people with epilepsy paying attention to states of mind and relieving stress may have a therapeutic effect. There are many anecdotal reports that stress increases the frequency of seizures.<sup>2-4</sup>

But is there any scientific evidence that stress may influence the activation of seizures? Although this is an underresearched topic, some evidence exists. Substantial numbers of patients report that the frequency of their seizures increases if they are exposed to stress (that is, an increase in excitement, tension, sadness, or other emotions caused by change in the patient's

internal or external circumstances).<sup>3-5</sup> Detailed studies of groups of patients, either with careful charting of life events and emotional states<sup>5-7</sup> or in the laboratory with electroencephalography,<sup>4,8</sup> show a definite relation between stress, emotional arousal, and frequency of seizures in some patients. For most patients more stress leads to more seizures, although in a few the opposite is the case.<sup>2,3</sup>

Changes in arousal in the brain lead to changes in excitability,<sup>3</sup> which may affect neuronal firing, particularly of those neurones that surround an epileptic focus and may affect further propagation of seizure discharge.<sup>3,9</sup> Other factors related to stress may be important—such as lack of sleep, consumption of alcohol, omitting drugs (deliberately or otherwise), and, most importantly, involuntary hyperventilation.<sup>4</sup> Some doctors have the clinical impression that epileptic seizures may start during periods of personal stress<sup>2</sup>; if the stress is not resolved this may help to continue the epilepsy. Epilepsy itself is stressful, and many patients become afraid of their seizures, so that a vicious circle of fear begetting seizures and seizures begetting fear is set up.<sup>2,3</sup>

If stress has a role in precipitating seizures then psychological treatment might help to prevent, control, or abort seizures. Much anecdotal, though little scientific, evidence supports this.<sup>3,10</sup> Many studies of the psychological treatment of epilepsy have been of single patients, often with unusual seizures. Treatment strategies used in published reports have often had a general relaxation element so that the specific effect of the treatment has been hard to determine or it has been difficult to separate treatment from placebo effects. Nevertheless, placebo effects themselves are also psychological and worthy of investigation: how does a placebo effect actually reduce the frequency of seizures? In some of these reports non-epileptic attacks may have been treated.<sup>11,12</sup> Carefully conducted trials are badly needed to delineate the relation between stress and seizures and to determine the effectiveness of psychological therapy. In these days of

pharmacological optimism for epilepsy, however, raising funds for such studies is difficult.

In treating patients with epilepsy attention should be paid to the emotions and stresses that patients endure; providing psychological as well as pharmacological treatment enables the doctor to practise a rewarding model of "whole person medicine."

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## Should clofibrate still be prescribed?

### *Further trials with harder end points are needed for all lipid lowering drugs*

Publication of the World Health Organisation trial of clofibrate (Atromid) reduced expectations that cholesterol lowering drugs might lower mortality from cardiovascular disease and raised unresolved questions about their role in increasing non-cardiovascular mortality.<sup>1,2</sup> Clofibrate significantly reduced the incidence of non-fatal myocardial infarction but did not lower mortality from coronary artery disease and actually increased total mortality by 47%. The increase did not arise from any single diagnostic group, and mortality ratios returned to unity or near unity after the drug was withdrawn. Since the clofibrate appeared to increase the risk of death should it still be available for treating lipid disorders?

There are four possible interpretations of the trial results. Firstly, the increase in non-cardiovascular mortality might have occurred by chance. This possibility seems remote, given the consistency of the trend over the trial period and its disappearance when clofibrate was discontinued. Secondly, the excess of non-cardiovascular deaths might have been a chance exaggeration of a trend seen in subsequent randomised clinical trials of lipid lowering drugs and to a lesser extent in primary prevention trials using lipid lowering diets only.<sup>3,4</sup> Given the small numbers of deaths, this interpretation is statistically plausible. Thirdly, increased all cause mortality in the intervention groups in this and other lipid lowering trials may be inversely proportional to the prevalence of coronary artery disease in the trial populations. Cardiovascular mortality rates were lower in the WHO clofibrate trial than in the other major primary prevention trials.<sup>3</sup> No excess of non-cardiovascular deaths occurred in the highest risk subset within the WHO clofibrate trial<sup>1</sup> or in two trials of secondary prevention in which clofibrate was used alone<sup>5</sup> or in combination with nicotinic acid.<sup>6</sup> A meta-analysis of all secondary prevention trials also showed a significant excess of non-cardiovascular deaths, but there was a trend to significantly reduced all cause mortality because of the predominance of cardiovascular deaths in the sample.<sup>7</sup> Fourthly, there may be specific differences between lipid lowering drugs in their effects on all cause and cardiovascular mortality; clofibrate may be significantly more "toxic" than other fibrates and other lipid lowering drugs.

Which of these interpretations, singly or in combination, was responsible for the results of the WHO clofibrate trial is

unlikely to be clarified because of the cost, scale, and difficulty of testing for mortality as an end point in randomised controlled clinical trials of lipid lowering drugs. Given these uncertainties, withdrawal of the drug would have been unreasonable. In effect, doctors have reacted to the trial by assuming that the fourth and worst interpretation was true. Clofibrate is now rarely prescribed in the United Kingdom; and when it is, it is presumably mainly for patients who started taking the drug before the trial results were published.<sup>8</sup> Should there be any remaining cause for concern?

Drugs intended to reduce the prevalence of cardiovascular morbidity and mortality are initially judged by surrogate end points such as their ability to alter serum lipid concentrations or to lower blood pressure. Organisation of a randomised controlled clinical trial with hard end points takes time, demands a large sample size, and is costly. Judged by the time scale required to organise and evaluate such trials, the patent life of drugs is short. Not all drug companies feel the need to carry out controlled clinical trials to assess hard end points and instead market their products solely on surrogate criteria. Two fibrates which have not been the subject of controlled clinical trials (bezafibrate and fenofibrate) are currently available for managing lipid disorders. Whether either shares the possible propensity of clofibrate to increase non-cardiovascular mortality more than other lipid lowering drugs remains uncertain. Remarkably, this has been no handicap to their commercial success since bezafibrate is the most widely prescribed lipid lowering drug in the United Kingdom.<sup>8</sup>

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (the "statins") are in the surrogate phase of their use. They are highly effective in reducing serum cholesterol concentrations, and their market share has expanded rapidly in the last five years. No convincing data on their ability to reduce cardiovascular morbidity or mortality or to affect all cause mortality are available.<sup>4,9,10</sup> The example of the WHO clofibrate trial must prompt an uneasiness that this class of drug is being vigorously marketed without results from the controlled trials currently in progress.

Advocates of the lipid hypothesis contend that sample sizes in the controlled clinical trials performed so far are not large enough to permit the use of death as an end point.<sup>11</sup> Interestingly, however, case-control and prospective cohort