been better investigated than almost any treatment for any cardiovascular problem this treatment has not yet become part of routine clinical practice – because many doctors prefer to move on to the new and unproved, which they hope will have dramatic effects, rather than to assimilate the relatively small benefits that are available from tested treatments.

The end of clinical freedom means that clinical trials and research in general have become more rather than less important, and when resources are scarce a greater proportion of them must be channelled into evaluation. If investigation and treatment are to be limited we must know which investigations and which treatments are valuable and which are not. New high cost investigational facilities (such as computed tomography a few years ago, or nuclear magnetic resonance scanning today) should be installed only in institutions able to evaluate them properly and with catchment areas adequate to provide the sort of patients to whom the new techniques will be applied when they become available to the average district general hospital. No new treatment (for example, coronary artery bypass grafting in patients without symptoms) should be allowed except as part of a properly conducted clinical trial, and such a trial would have to be conducted on a multicentre basis so that a wide variety of patients and medical skill would be included. Before they can be approved for prescription on a large scale new drugs need to be tested not only for efficacy but also in comparison with old drugs; a new and expensive drug can be accepted only if it is superior to an older and cheaper one. Training in evaluation techniques must form part of the education of any potential consultant; only by so doing will consultants carry through their career the habit of inquiry and scepticism that will be essential in the more restricted financial atmosphere that lies ahead.

Clinical freedom died accidentally, crushed between the rising cost of new forms of investigation and treatment and the financial limits inevitable in an economy that cannot expand indefinitely. Clinical freedom should, however, have been strangled long ago, for at best it was a cloak for ignorance and at worst an excuse for quackery. Clinical freedom was a myth that prevented true advance. We must welcome its demise, and seize the opportunities now laid out before us.

References
angiogram with a view to coronary artery bypass graft surgery. In 1983, clinical freedom was the accepted philosophy of medical practice: it was the doctor’s duty to do whatever he believed to be right for an individual patient. By and large, patients were happy to accept their doctor’s recommendations. I argued that new treatments, inevitably more expensive than their predecessors, could no longer be afforded. Clinical freedom was a myth, a cloak for ignorance and its demise was to be welcomed. Treatment should be based only on the result of clinical trials. The call was in large part successful, but 27 years later I suspect that clinical freedom must be reinvented.

In my BMJ editorial I did not—sadly—invent the phrase ‘evidence-based medicine’, but that is what I was talking about. The phrase did not enter the medical literature for another 9 years and even in that time much had changed. The year 1983 was a year that marked the birth of modern clinical trials: until then there had been trials, some good but mostly by modern standards hopeless, but after that the science of the trial gradually evolved.

Prior to 1983 major advances such as the introduction of penicillin had not needed anything more than simple observational studies and the landmark Medical Research Council (MRC) trial of streptomycin had demonstrated the value of this drug for tuberculosis in a trial involving only 100 patients, a number dictated by financial stringency rather than by statistics. The BMJ had published a trial comparing home and hospital care for patients with myocardial infarction that included a mere 260 patients, and trials of ß-blockers after myocardial infarction (then the hot topic in cardiology) involved only 100 or 200 patients.

The importance of trial size had been well known to statisticians, but for some reason they had not been able to educate the medical profession until about 1983. Then came the ISIS-1 trial of atenolol after myocardial infarction (1986, 16,000 patients) and the ISIS-2 trial of streptokinase (1988, 17,000 patients). Clinical trials were largely a British affair, the Americans were shown to improve the symptoms of heart failure but to increase the death rate. A patient might well choose a shorter life with fewer symptoms.

Eventually, the meta-analysis of multiple trials became the gold standard. Adding trials together is as if that were a new concept. Using multiple endpoints added together to increase the power of a trial was equally dangerous, for the effect on one endpoint might be beneficial, and on another it might be harmful. A general view developed that death was the only true endpoint, and then there was debate about what manner of death should be included in trial results. Even that might be over-simplistic and for example, several agents have been shown to improve the symptoms of heart failure but to increase the death rate. A patient might well choose a shorter life with fewer symptoms.

From the early 1990s, the Americans accepted the importance of clinical trials, and the number of patients in trials (and the number of trial acronyms) mushroomed. In 1996, Sackett et al.8 tried to define evidence-based medicine as ‘the judicious use of current best evidence in making decisions about individual patients (which means) integrating individual clinical expertise with the best evidence from systematic research’. Clinical expertise meant ‘the proficiency and judgment that clinicians acquire…in the thoughtful identification and compassionate use of individual patients’ predicaments’. While the medical world was happy to seek the best evidence, Sackett’s emphasis on the management of individual patients was lost sight of, and the randomized trial became the gold, if not the only, standard for judging whether a treatment does more good than harm.

So clinical trials became larger and more expensive, and almost beyond the financial reach of even the pharmaceutical industry. Attempts were therefore made to devise ways of obtaining statistically significant results from small studies, using techniques such as surrogate and multiple endpoints. The problem with surrogate endpoints was that what seems to make sense is not always true, and the best example of this was the Cardiac Arrhythmia Suppression Trial (CAST) of 1989, which was based on the idea that if patients with coronary disease die of arrhythmias, suppressing the arrhythmia would prevent death. The CAST and other trials showed the reverse to be true.

Just to confirm the triumph of hope over experience two more drugs introduced on the basis of surrogate endpoints have come to grief. Sibutramine was hoped to reduce heart attacks by controlling obesity: it certainly caused weight reduction, but heart attacks increased. Rosiglitazone was developed and licensed to control the harmful effects of Type 2 diabetes, but it too increased the risk of a heart attack and the BMJ published an editorial headed ‘Surrogate endpoints are not enough, robust evidence of benefits and harms is needed’—as if that were a new concept.
in principle useful, but quite another to know which patient to treat and what dose of which drug from a family of drugs should be used. Unthinking meta-analysis is the equivalent of adding apples to oranges and describing the effects of fruit—that might have worked in James Lind’s trial of oranges and lemons in scurvy, but it would not apply to many modern situations.

Worse, meta-analyses have been misleading. One such analysis of several trials suggested that intravenous magnesium and nitrates reduced fatality in acute myocardial infarction, but a single large and definitive trial, ISIS-4 showed that both were ineffective. A review of 19 meta-analyses that were followed by 12 definitive trials showed that without a proper trial the meta-analysis result would have led to the adoption of ineffective treatment in about one-third of the cases, the rejection of a useful treatment in another third, and the adoption of a useful treatment in only about one-third.

A clinician attempting to practice evidence-based medicine has to decide whether the results of a trial apply to his individual patient. Clinical trials often exclude the elderly, and usually exclude patients with other diseases. The only way to be certain of the relevance of the results of a trial is to maintain a register of all the patients seen who might have been included, whether they were actually included or not. The findings of such trial registers, which are rare, are not encouraging. In the TRENT trial of nifedipine referred to above, all the patients admitted to the participating hospitals with acute myocardial infarction were logged. In the group randomized to receive nifedipine, the fatality rate was 6.7% compared with 6.3% in the group given placebo. But in ~50% of patients who were not randomized, the fatality rate was 18.2%. Similarly, in a trial comparing angioplasty and coronary artery bypass grafting in patients with stable angina, a trial register showed that only 3% of possible patients were randomized.

How, then does the clinician decide which clinical trial to apply to his patient? One begins to think that we should be talking about opinion-based, not evidence-based, medicine.

Having said all that, we cannot do without clinical trials; the important thing is to recognize their limitations. It would be helpful if we could assume that all the drugs in one class (β-blockers, angiotensin converting enzyme inhibitors, anti-arrhythmics) were interchangeable, but there is plenty of evidence that this is not so. For example, amiodarone is probably the best anti-arrhythmic drug currently available, but it causes an unpleasant series of unwanted effects. Its derivative dronedarone was shown in a study that compared the two drugs to have less unwanted effects, but to be a less-powerful anti-arrhythmic.

The recognition of unwanted effects is one of the most important results of clinical trials. The anti-obesity drug rimonobant was licensed in several countries on the basis of a series of small trials, which showed that it was effective in reducing weight and in reducing other risk factors for coronary disease. A large (18,000 patients) trial was set up to find out whether a collection of cardiovascular endpoints would be reduced, and the trial had to be stopped prematurely—and the drug withdrawn from use—because of an unexpected finding of drug-induced psychiatric and neuropsychiatric unwanted effects.

Thus, there is no alternative to clinical trials for finding out whether an individual drug is safe and effective, but these answers still do not help the treatment of individual patients. These problems are exemplified by the use of warfarin in elderly patients with atrial fibrillation. The main risk of atrial fibrillation is stroke. Most patients with atrial fibrillation are elderly, and 12% of the >75-year olds have atrial fibrillation. The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) randomized nearly 1000 patients aged >75 to treatment with warfarin or aspirin and the stroke rate was halved (1.8 vs 3.8%) in the warfarin group. In this study the risk of bleeding was not much different between the two groups, but other studies have suggested a significant bleeding risk with warfarin. No register was kept in association with the BAFTA study, so it is difficult to judge just how applicable its results are to the generality of aged patients. But there is no doubt that the old have multiple diseases and are necessarily on polypharmacy, and their immobility can make accurate control of their International Normalised Ratios (INRs) difficult and therefore make warfarin use more dangerous and possibly less beneficial. The only option a doctor has when deciding on treatment for an elderly patient with atrial fibrillation is to use his clinical judgement (i.e. take a deep breath and guess) about the relative risks and benefits of warfarin.

In 1983, I was worried about the increasing costs of new treatments and ‘the financial limits in an economy that cannot expand indefinitely’, and I called for evidence. We have a lot more evidence, even if it is not always easy to interpret. Medical costs have become higher and the funding has increased considerably, but the general statement holds true. The overall picture is, however, more complex. The evidence has led to a multiplicity of guidelines, and to the National Institute for Health and Clinical Excellence (NICE). NICE guidelines do not always find agreement among specialists. Although most would accept that guidelines are for the obedience of fools and the guidance of wise men, primary care trusts (PCTs) are unwilling to fund treatments not recommended by NICE, and we now have the bizarre situation where the government has made available to PCTs funds specifically for cancer treatments not approved by NICE. At the same time clinicians are dubious about using treatments
not included under the NICE umbrella. Treatment has become protocol driven, and in a standardized service doctors feel discouraged from commitment to individual patients. This will almost certainly be accentuated by the latest re-reorganization of the National Health Service with its inevitable transfer of services to the private sector.

So we seem to have the perfect storm, where a meeting of evidence-based (which we ought to call opinion-based) proscriptive guidelines, mechanistic doctors and financial control have come together to contribute to the demise of the responsibility that doctors used to have for individual patients. We need to change medical culture in such a way that doctors can use their opinions about published evidence to select the best treatment for each individual patient. We need a return to clinical freedom.

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References