Hither neurology: research

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Abstract

Neurological disability may be prevented, or it may be alleviated if prevention is impossible or ineffective. Research into prevention and alleviation can be "laboratory" or "clinical", the latter being no less scientific than the former. All proposed treatments must be properly evaluated to ensure that effective interventions are widely adopted and ineffective ones abandoned. Unless an intervention has a major effect on outcome (which most do not), the most efficient assessment is by random allocation of patients to the new intervention versus the old. Although there were, and still are, forces opposed to the proper evaluation of treatment, there are strong economic clinical arguments in its favour, which will lead to appropriate targeting of scarce health resources.

"One should be delightfully surprised when any treatment at all is effective, and always assume that treatment is ineffective unless there is evidence to the contrary". A L Cochrane, Effectiveness and efficiency (1971).

Some equate science, and therefore research, with laboratory based activities. There is an argument that rats and molecules provide scientific solutions to human problems and the results can be applied by clinicians, who are themselves seldom "scientific". One hears talk of clinical research as though it is something other than science. This view may come from: basic scientists most of whom are not medically qualified and know little, and may care even less, about the difficulties, rules and solutions of clinical science; from clinicians who feel intellectually inferior to basic scientists and find solace, and perhaps profit, in the "art" of medicine; and from clinicians who have become bewitched by basic scientists, join them in their laboratories and yet struggle to keep up because of their clinical commitments.

I must confess to being intimidated by basic science and basic scientists but only because I do not have their training, aptitude or background; I have the same problem with wine tasting. Of course, this does not mean that I am against basic science, or wine tasting, far from it. What I am against, however, is the uncritical application to patients of ideas, hypotheses and solutions generated by basic

scientists (and others) without proper evaluation; what works in the rat does not necessarily work in humans. The application of treatments and diagnostic techniques which, according to the basic scientists, or others, ought to work but do not, has caused harm while the introduction of treatments and diagnostic techniques which really work (according to the clinicians), but no one knows why, has been beneficial. An example of the former is the use of high concentrations of oxygen in premature babies which seemed a good idea but turned out to cause retrolental fibroplasia,¹ and an example of the latter is the use of electroconvulsive therapy to alleviate depression.² Many of the recent spectacular successes in medicine have come from basic and clinical scientists working together, neither ignoring each other nor attempting to do each other's work; patients provide the problems, which clinicians identify and place in perspective, basic scientists find possible solutions which are then tested on patients by the clinicians. Beta blockers, thrombolytics, H₂-antagonists, CT scanning and foetal ultrasound were all introduced this way.

With a few notable exceptions, clinical neurologists (and clinicians generally) do not have the training, facilities or time to build up and orchestrate a large laboratory-based research programme. Usually this is carried out much better by full-time basic scientists working with neurologists, maybe within the same university department or pharmaceutical company. Most clinicians tend to be much more comfortable with clinical research because they are familiar, and competent to deal with patients. Clinicians are capable of meeting the intellectual demands of any sort of science, clinical or basic, if the criteria for United Kingdom medical school entry are anything to judge by. It seems a mistake for a young neurologist to work for a couple of years in a laboratory and then obtain a consultant position looking after countless patients without any prospect of working in a laboratory again; but often this is precisely what happens. Surely it is preferable to give equal encouragement and prestige to young neurologists to do clinical research, at least in the sense of evaluating diagnostic techniques and treatments, because that is what they will be able to do as consultants, given a small amount of time, a microcomputer, and reasonable contact with other researchers.

The main contribution of most clinical neurologists is our ability, and facilities, to do clinical research with our patients. For

neurological disability, our major current objectives must be to evaluate rigorously the prevention, cure, alleviation and palliation of the common disabling disorders such as stroke, epilepsy, multiple sclerosis and Parkinson's disease. Whether the suggestions, often from the basic scientist, are concerned with vaccines (such as, polio), drugs (such as, vigabatrin), surgery (for example, brain tissue transplantation), psychology (for example, cognitive rehabilitation), physiotherapy (such as the Bobath technique), or service rearrangements (for example, stroke units), in the end they all require proper evaluation. Competent evaluation is the greatest contribution clinicians have to offer both science, and their future patients.

WHY BOTHER WITH EVALUATION?

Evaluation is fashionable, particularly among managers whose sights may be set no higher than "before and after" comparisons of cost which is so much easier to measure than quality of outcome. There are, however, a number of valid scientific reasons for encouraging evaluation, which is clinical research into the care of patients.

1 Limited resources should be appropriately directed. What is deemed appropriate depends on whether one wishes to concentrate on broad brush public health measures (such as, vaccination or changing the nation's diet), on more focussed efforts with individuals (for example, treating patients with severe hypertension), or on a combination of both. However, before any such philosophical and political decisions are possible it is necessary to know what works, how much it costs, what are the adverse effects, and what is the overall likely outcome if the treatment is introduced into routine clinical practice. We must conserve resources by rejecting the useless, while implementing useful treatments.

2 Clinical practice should be directed appropriately so that clinicians neither waste their time nor expose patients to unnecessary risk by providing treatments, of any sort, which are ineffective, even though they should theoretically work. For example, careful evaluation has quite rightly inhibited the uncritical introduction or continuation of extracranial-to-intracranial by-pass to prevent stroke,³ bed rest to improve the outcome of twin pregnancy,⁴ the use of a new "improved"

suture material for episiotomy,⁵ hyperbaric oxygen to improve the prognosis of multiple sclerosis,⁶ haemodilution for the treatment of acute ischaemic stroke,⁷ and antifibrinolytic drugs to reduce the risk of rebleeding after aneurysmal subarachnoid haemorrhage.⁸

3 Large and unacceptable variations in clinical practice must be reduced. It cannot be right to treat the same patient in one way in one place and in quite another way in another place. Yet this is what often happens in clinical practice,⁹ as it does in legal practice (table 1). Such variation is not usually a reflection of ignorance on the part of the clinician (or judge), but lack of evaluation combined with inadequate data. Without proper evaluation, the clinician has to make a decision whether to give, or not to give, a particular treatment to a particular patient and may jump one way or the other depending on whim, the result in the previous patient, philosophy, pressure from managers, pressure from peers, pressure from salesmen, or possibly profit. After proper evaluation which can influence clinical practice there is, rightly, much less room for manoeuvre and for non-scientific influences on which patients should receive what treatments.

4 Even at worst, evaluation protects us from the ridicule of future generations. I would not want any treatment that I introduced to be included in books such as "Need your doctor be so useless?"¹⁰ nor used as teaching material about how *not* to do something, such as the epidemic of unnecessary tonsillectomy in the middle of the twentieth Century.¹¹

WHY ARE NEW TREATMENTS NOT WIDELY ADOPTED?

There are several reasons why a new treatment is not taken up in routine clinical practice: the theoretical basis may be regarded as so unsound that no evaluation is carried out (for example, copper deficiency as a cause for atheroma); the advantage may be perceived (rightly or wrongly) as rather modest, and not enough to outweigh the risks (such as, carotid endarterectomy in the prevention of stroke); financial and political pressure, or just fashion, which may explain the controversy surrounding the introduction of front seat belts and the continuing controversy about the introduction of rear seat belts, government policy on smoking, and heart transplantation; the innate conservatism of most doctors (for example, the difficulty of introducing very early operation for aneurysmal subarachnoid haemorrhage); and lastly prejudice against the investigator who is introducing the treatment.

All these reasons for doing nothing are reinforced when a new treatment is suggested if the "experts" cannot agree with each other, and "experts" usually do disagree when evaluation is inadequate. After one, or preferably more, excellent randomised clinical trials it is very difficult for anyone to resist, for any reason, the introduction of an effective treatment. For example, after decades of debating on the inadequate data, thrombolysis was even-

Table 1 The chance of a prison sentence for criminal damage: 17-20 years old

Powys	5.1%
Surrey	5.9%
Suffolk	8.1%
Norfolk	8.3%
Gloucestershire	9.8%
Nottinghamshire	21.1%
South Yorkshire	21.9%
Northumbria	25.3%
Kent	26.1%
Hertfordshire	31.6%

Home Office statistics for Crown courts in 1988 (report from *The Guardian* 23 January 1990).

tually introduced as the routine treatment for acute myocardial infarction as a result of two very large clinical trials which overwhelmed any theoretical, political, financial or other arguments.¹² Of course, to influence clinical practice, any evaluation has to be scientifically convincing and free from conflict of interest. For drugs, there is no question that the most cost-effective and convincing method to compare treated and untreated patients is the randomised trial. Of necessity, economic and political policy must make do with unreliable "before and after" comparisons¹³ but in medicine we have the great advantage of randomisation. When randomisation is not used, there is so often continuing and sterile argument such as whether consultation with a neurologist improves the outcome for patients with non-organic headache. Although the general practitioner consultation rate for headache may fall after seeing a neurologist,¹⁴ the total number of consultations does not.¹⁵ However, we do not know what this means as these comparisons were "before and after" the neurological consultation, whilst headaches may remit spontaneously. Furthermore without any comparison between neurologists and, for example, general physicians we do not know whether neurologists are the best type of specialist to empty general practitioners' surgeries if that is the outcome of interest. Of course, in practice, curing the headache is more important. Extraordinarily, these two studies are almost the only ones where the effectiveness of neurologists has been examined so it is hardly surprising that we still do not know whether neurologists are really effective, and if so whether they are more effective than general physicians. Naturally, neurologists themselves believe this to be the case, at least for the management of rare neurological disorders rather than common diseases such as stroke which so many neurologists seem to want to leave to other people.

Unfortunately, although random allocation is now the accepted method for the evaluation of drugs, there is still resistance to its use in the evaluation of surgery and even more for the evaluation of most of the treatments used in neurological rehabilitation. This is particularly unfortunate since surgery and rehabilitation can be very costly, and even dangerous, and it is an indefensible double standard to insist on randomisation for the evaluation of drugs but not of other treatments. However innovative, and theoretically attractive, treatments may not be taken up into clinical practice if they are not properly evaluated in randomised clinical trials by clinical scientists whose business it is to test out whether theories work in practice. Alternatively, a theoretically attractive treatment may be used for years before a proper evaluation shows it is useless. As Thomas Huxley wrote, "the great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact".¹⁶ In this context, the ugly fact may be a competently performed but negative clinical trial on an adequate number of patients. Or, if there are several clinical trials addressing the same issue, a competently performed but negative overview (or meta) analysis.

RESISTANCE TO EVALUATION

Despite its vogue, proper evaluation is constantly under threat from several directions. This is not the place to debate in detail the ethics of randomisation, but there is no doubt that ethical arguments can inhibit randomised trials if the new "improved" treatment *must* be given because it is *bound* to work (that is, theory says it will). This may have been true for the very few treatments which have major and obvious effects (for example, penicillin for meningococcal meningitis) but most treatments have modest, and yet potentially useful, benefits as well as modest, and yet potentially harmful, adverse effects and the balance of benefit and harm cannot be predicted from theory alone. Moreover, non-randomised comparisons provide no guarantee that like (patients) are being compared with like.

The great ethical advantage of randomised trials is not just for future patients but also for patients in the trial; not only do patients in randomised trials tend to fare better than expected (perhaps as a consequence of selection of better risk cases for the trial, better ancillary treatment during the trial, and a mistaken gloomy view of the natural history before the trial) but also those randomised to the old treatment will be spared the adverse effects of a new treatment which simply does not work, or is so unpleasant it cannot be used in routine clinical practice. Without randomisation, a toxic and/or ineffective treatment which ought to work may be given to thousands of patients before it is abandoned (for example, tonsillectomy for sore throats) or an effective treatment can be abandoned in error so denying thousands of patients an improved prognosis (which nearly happened with thrombolysis for acute myocardial infarction). Clumsy attempts at detailed "informed consent" may be so distressing to patients that they will not enter randomised trials and become so confused and anxious that they cannot even decide which treatment they want from among the alternatives offered.

Basic scientists may sometimes be so overwhelmed by the elegance of their solutions to human problems that they insist that the crucial step of proper evaluation can be omitted. The task of the clinical scientist is to resist such pressure and to remind the basic scientist what Thomas Huxley had to say, and indeed what Richard Asher, that consummate general physician, wrote: "One of the most important things about treatment is that it should *be* effective—not merely that it *ought* to be effective. A remedy which is known to work, though nobody knows why, is preferable to a remedy which has the support of theory without the confirmation of practice".¹⁷ Also, some basic scientists tend to deride clinical research yet they may dominate the research funding bodies so attracting disproportionate funding to basic rather than clinical science. Of greater concern is that clinical trials can take so long that the basic scientists have changed their proposed treatments several times before the first one has been properly tested. Another and irritating problem, for the clinical researcher, is the basic scientist who simply uses the wrong model to

predict the consequences of, and solutions to human diseases.

It can be difficult to obtain funding for randomised clinical trials of treatments like coronary care, physiotherapy, surgery, aspirin, or service rearrangements when such endeavours are considered "unscientific" by the research councils, or "not profitable" by industry, or "someone else's business" by health authorities. Such problems are compounded where there is no international source of funding for international multicentre trials, other than the multinational pharmaceutical companies. Therefore, if multicentre international trials are required to obtain large numbers of patients quickly there is little hope of funding unless the treatment is a patented drug. Institutions such as the European Community ought to provide the resources but, so far, they have not.

The NHS reforms may be very dangerous for clinical research, especially for the evaluation of treatment, unless the purchasers of care (the health authorities) and/or providers (hospitals) see it as part of their remit to evaluate treatment rather than merely to purchase or provide it. The market solution would be to make it clear, particularly to the providers, that investment in evaluation would be to their advantage since the introduction of a cost-effective treatment would attract contracts from the purchasers of health care in the competition with other providers who may be using ineffective, out-dated or costly treatments. The problem is that unless such a treatment is kept a commercial secret it would be shared by all the competing providers because clinical scientists are in the habit of sharing their ideas and results. Indeed, it would be unethical if a new treatment discovered by a provider hospital was kept secret so that hospital could obtain a contract, and yet this is what the NHS reforms might in practice encourage. An acceptable alternative would be to take evaluation out of the purchaser/provider relationship by insisting that it is funded either centrally by Government, or, by top slicing a proportion of the budget of a purchasing authority and insisting it is spent on research. Furthermore, the NHS reforms may be damaging if every last item of the currently hidden costs of clinical research is charged for (for example, providing a copy of a patient's discharge summary to a researcher), if academic clinical departments are seen as unprofitable and unaffordable luxuries, if potential clinical academics are tempted by inflated salaries to do just clinical work for institutional or personal profit, and if there are so few medical staff that there is simply no time for research.

Paradoxically, the mushrooming of multicentre clinical trials, and now overviews, may reduce the perceived contribution of an individual clinician so much that being involved as a minute cog in a large evaluation machine becomes profoundly unattractive. One only hopes that this problem can be alleviated by making multicentre trials less arduous, more fun to take part in, and by giving them an educational component. Personally, I

learnt a great deal about epilepsy by my involvement in a multicentre trial of anticonvulsant drug withdrawal and I hope that others learn about cerebrovascular disease by their involvement in the trials which I organise. Clinicians find it hard enough to find the time to contribute to multicentre trials already and might abandon them completely if clinical science is "rubbished" by basic scientists, if the clinicians are overwhelmed by routine clinical work, and if they are not given credit for being the resource for the proper evaluation of treatment for their patients. Without clinical scientists there would be a jungle of untested and toxic treatments, some effective and others ineffective, and no-one would know which treatment to use although, as clinicians, they would have to do something.

Perhaps the main distinction between the basic scientist and clinician is that the former can admit to uncertainty and do an experiment, while the latter can admit to uncertainty yet has to treat the patient. However, the scientific clinician can take advantage of uncertainty when it is as ethical, or even more ethical, randomly to allocate the patient in a clinical trial which is large and effective enough to resolve the treatment dilemma.

THE MOVE TOWARDS EVALUATION

Given the need to evaluate new treatments so that clinical practice is improved, and despite the difficulties, it is worth emphasising that there are several strands which are now strongly encouraging evaluation. Not only is evaluation fashionable among managers (although as noted above they need to be educated how to do it properly), but clinical trial methodology has become better, simpler and cheaper. Indeed, the fact that randomisation is an option makes evaluation very cost-effective in a climate in which resources for everything are limited. The challenge is to persuade the purchasers and providers of health care that evaluation must be considered in their budget so their resources can be directed appropriately. Also, there is increasing patient pressure for proper evaluation and this is worth encouraging. It is very cheering to hear patient representatives on ethical committees criticising non-randomised treatment comparisons as being unscientific and therefore unethical, and medical charities encouraging their members to enter randomised clinical trials.

There is no doubt therefore that there are plenty of forces to be harnessed when the going gets tough and the demoralised and underfunded clinical scientist starts dreaming of early retirement, the golf course or private practice. One must not be daunted by the cost of clinical trials because they do seem to be cost-effective in strictly economic terms, even when carried out in North America,¹⁸ nor by the consequences of introducing new treatments which do not necessarily have to be more expensive than the old (for example, early mobilisation after myocardial infarction, phenothiazines for schizophrenia, streptokinase for acute myocardial infarction, aspirin to prevent stroke, no bed rest for twin pregnancy,

Table 2 Association of Medical Research Charities; expenditure on biomedical research 1989-90

	£ million
Cancer charities*	85.0
British Heart Foundation	14.6
Arthritis and Rheumatism Council	11.0
Cystic Fibrosis Research Trust	2.6
Multiple Sclerosis Society	2.4
British Diabetic Association	2.1
Muscular Dystrophy Group	1.9
Chest, Heart and Stroke Association	1.0
Parkinson's Disease Society	0.9

*Cancer Research Campaign, Imperial Cancer Research Fund, Ludwig Institute for Cancer Research, Tenovus Cancer Fund.

no bed rest to prevent post lumbar puncture headache, and angioplasty rather than surgery to relieve certain arterial obstructions).

Indeed, in the United Kingdom the National Health Service (NHS) gives us a particular advantage in clinical research because health care is free at the point of delivery, and therefore patients are not financially disadvantaged by being in clinical trials, and it is equally available to all patients. In the NHS, medical records are held by general practitioners, with whom almost all patients are registered, and these records follow the patients when they move. This provides a unique file including hospital letters and discharge summaries as well as the general practitioner notes. These can be used for detecting outcome events such as stroke, or antecedent events such as vaccinations or fractures. Moreover, follow up can be arranged with general practitioners without patients necessarily having to go to a hospital clinic. In the UK, doctors are still trusted because they do not, usually, make a direct profit out of their patients who are likely to collaborate with well explained sensible and necessary clinical research.

Clinical research is still regarded as a reasonable use of NHS resources to be added to those provided by third party sponsors such as universities, research councils, industry and charities. However, such sponsors cannot fund everything, such as additional follow up appointments or investigations, which may be more than is strictly required for routine patient care. The new NHS reforms might sweep away these advantages, or lead to attempts to cost every last item so sinking clinical research in complex demarcation disputes.

WHO WILL PAY?

Many countries cannot, or will not, finance any medical research at all so in the UK we are fortunate to have a long and secure enough

tradition of medical research to ensure that, come what may, it will continue. However, the pattern of funding is changing¹⁹ with relatively more coming from industry and medical charities and relatively less from Governmental sources through the research councils and universities. The disadvantages of leaving matters to the industrial market place are that research will be done only for profit rather than being led by scientific and public health priorities; underfunded clinical departments will be tempted into patented drug research which they do not really want to do just to keep solvent; clinical researchers will be tempted away from the universities and NHS to industry; non-patented interventions will be ignored; and sometimes the results, or their interpretation, will be presented primarily to suit the marketing rather than the medical department of the sponsoring company. Of course one cannot, and should not, expect a company responsible to its shareholders rather than to the public health to do anything other than strive for profit; it would be unrealistic to expect Roche to support research into behavioural treatments of insomnia when they manufacture hypnotics.

At the same time, the medical charities do not have the resources to fund truly major research, except perhaps for the cancer charities, and in any event their success is driven so often by forces which tend to favour cancer and children rather than public health priorities which might, perhaps, favour neurological disorders, or the elderly (table 2). So it remains with Governmental agencies to identify good clinical research and to allocate resources based on a mixture of public health demands and what is scientifically likely to succeed. In other words, there must be a cooperative plan rather than an unmanaged market place with short term commercial objectives. This is a major national challenge.

In the meantime, clinical scientists have their own challenges since there is no shortage of treatments which need evaluating (table 3). It is our task to encourage research into evaluation of current practice, of the large number of new ideas coming from basic scientists and others, and of what our managers would like us to do in the future. It is an exciting time for clinical research so, "hither clinicians" who are interested. Do not be overly intimidated by the basic scientists; overwhelmed with routine clinical work, tempted by the pharmaceutical industry, excessive personal profit or an easy life.

Table 3 Interventions being evaluated or requiring evaluation in the Edinburgh department of Clinical Neurosciences

Nurse practitioner for multiple sclerosis patients
Family care officer for motor neuron disease patients
Comprehensive stroke service
Programmed investigation unit
District based neurology clinics
Aspirin/heparin/both/neither for acute ischaemic stroke
Carotid endarterectomy
Essential amino acids for motor neuron disease
Cognitive rehabilitation

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