Leading articles

Evidence based medicine

Traditionally the physician's absolute right to decide what treatment any individual patient should be offered has been the Holy Grail of clinical practice since the earliest of time. Such a decision has clearly always been influenced by individual physician experience, and the presented or published results of fellow practitioners. The first medical research trials to investigate the use of patulin treatment in the common cold 1943–44 (double blind controlled trial with quasi randomisation)[1] and of streptomycin in tuberculosis 1947–48 (randomised control trial but with no placebo)[2] heralded in a new era. Bradford Hill is reported to have been worried "that doctors would be unwilling to relinquish the doctrine of anecdotal experience" when he proposed the concept of randomised clinical trials.[3 4] The randomised clinical trial has become the "gold standard" by which the choice of treatment and evidence to support its use is now judged. The physician inevitably must ultimately decide, based on knowledge of the patient's overall health, both physical and emotional, as to whether such trial evidence should be applied to that particular individual. It has become fashionable and indeed commendable to demand the evidence base for all medical actions, using the data from any randomised clinical trial and systematic overviews. The *British Medical Journal* and the American College of Physicians indeed created a team who have worked together to produce an evidence formulary on the prevention and treatment of common ailments, including areas of uncertainty and doubt,[5] for example, in atopic eczema.[6]

Almost inevitably there has been a backlash with challenges made to the reliability and applicability for the individual of evidence based on randomised controlled trials and overviews.[7] Goodman[8] argues that "the presumed opinionated dogma of the expert" may have been replaced by dogma from a different source. Much of the criticism revolves around known trial publication bias (for positive results), the lumping of trials of various sizes and quality into meta-analyses (each with unknown inbuilt flaws), and then the extrapolation of results back to the individual patient. Those who carry out and believe in the value of meta-analyses have argued publicly about optimal methodology, giving support to their detractors.[8 9]

Indeed there appear to be two competing factions who are waging a fairly public war on the whole question of evidence based medicine. Those who believe that randomised clinical trials (preferably double blinded), meta-analyses, and consensus conferences are the only sound basis on which therapeutic decisions should be made,[10] compete for publicity with those who believe that trials often ask over simple questions, and in a sense "dumb down" the complexity of human illness. They believe that the quality of individual trials included in overview analyses is not scrutinised carefully enough, and too much emphasis is placed on significant statistical tests, when the basic data may be less than robust. Kleinert expressed the view that "the modern trend to search for precise answers in the form of numbers and probabilities can have only a limited role in human sciences such as medicine".[11] Toxicity may be overlooked in trials and the question of general applicability of findings to groups of patients not involved in the original studies inadequately addressed. They claim that if negative result trials are not published, a consequent highly biased picture on the effect of any particular intervention emerges.

However, greater public awareness and education on health matters, coupled with access to information (increasingly via the Internet) is now leading to much greater challenge to the perceived wisdom of doctors. Parents especially, wanting the very best for their sick child, but being emotionally so involved, need guidance on the evidence to support recommended therapy. Challenges to recommendations are too frequently associated with formal complaints and/or litigation, and it is essential that we, as practitioners try to take control of the situation and prevent any worsening of this critical state of affairs.

Sniderman[12] has summarised the strengths and weaknesses of trials and overviews, and recommended ways in which these valuable instruments could be made more robust. Wherever possible, trials should be all inclusive with minimal exclusions, and be total population based wherever possible. They should always be reported, no matter whether the results are positive or negative. Very clear declarations of conflicts of interest are essential, especially for studies sponsored by the pharmaceutical industry. For both meta-analyses and consensus conference all results and/or opinions must be included, to try to minimise bias and/or the excess influence of any particular individual or opinion.

Haematology and oncology has been the subspecialty of paediatrics, which over the last 30 years has been involved most actively in randomised control trials, and in which more recently there has been production of a flurry of clinical guidelines and overview analyses. The experience of the Medical Research Council Leukaemia Trials can possibly inform the current debate. During the 1970s the MRC Childhood Leukaemia Working Party brought together an increasing number of specialists who entered their patients into a series of randomised control trials, based on individual drug responses, tested largely in the USA in phase I and II studies during the 1950s and 1960s. The template which had developed for acute lymphoblastic leukaemia (ALL) consisted of a three drug induction period, central nervous system directed therapy, and at least two years of continuing therapy. Innovative approaches trying to improve on disease control proved disappointing in the 1970s in the UK until direct adoption of the American Children's Cancer Study Group Trial 162(1A).[13] This trial entirely reproduced the American results with over 50% five year event free survival.[13 14] It was a single arm study, not a randomised trial. The drugs used were not different from those used previously, but adherence to protocol with emphasis on physician, parent, and patient compliance and more continuous sustained delivery of drugs appeared to be the key elements. Some caution must be expressed with regard to these conclusions, as there must always be an element of subjectivity if such aspects are not themselves part of a randomised trial. After one year of this particular study paediatricians felt comfortable with the approach and its early promise and introduced two randomised variables: (1) for intensification of induction with the addition of an anthracycline (two doses only on days 1 and 2 of therapy or none); and (2) for duration of therapy (two versus three years). Between 1980 and 1984, 829 patients were entered into this UKALLVIII

study and trial, but this still represented only about 70% of eligible UK patients with childhood ALL. The accrual figures for the most recent ALL trials are approximately 90%.[15] Most of the remaining patients are treated according to the protocols but not registered in the trial for a variety of reasons. Such near universal application makes selection bias less of a worry, and makes the results more generally applicable to any individual child who develops ALL than was the case in the earlier trials.

The randomised components of UKALLVIII yielded interesting results. Use of the daunomycin in induction yielded a significant reduction in relapses, but this was matched by an excess of early infection deaths (secondary to more profound myelosuppression).[14] This early death rate was considerably reduced in the next trial (UKALLX) as a result of physician and family vigilance, coupled with improved aggressive management of bacterial sepsis.[16] Indeed the parallel development of many support services has reduced the risks of what has become ever increasingly intensive therapy for leukaemia and cancer in childhood.[17] Interestingly this trial involved the largest number of patients ever randomised between three and four induction agents, so that in overview analysis it swamps all other data. Consequently the overview is not reliably able to provide independent support for the benefit of induction anthracycline usage. There has since been no thorough randomised trial addressing this question. Worries about the late cardiac effects of anthracyclines subsequently led to the removal of induction daunomycin in the UK, in order to reduce overall exposure to this agent to a total dose of less than 200 mg/m^2. Use of anthracyclines in induction is however, now advocated worldwide for high risk patients. In retrospect the decision to withdraw it from the UKALLXI protocol may have been premature and resulted from trial participants having a real worry about long term effects in their patients. So much then for those involved in randomised trials not worrying about toxicity and being insensitive to their patients' problems.

The duration of therapy question also showed a benefit in terms of disease control for longer treatment, but this was associated with increased remission deaths, especially at that time from measles and pneumonitis, two problems which are both potentially preventable. Those who stopped treatment at two years and subsequently relapsed appeared to be retrievable by further therapy,[14] which meant that overall there was no benefit in terms of long term survival for those receiving the longer course of initial therapy. Subsequent trials throughout the world adopted a standard two years of treatment, but meta-analysis has suggested a real benefit for longer treatment, particularly if the infection risk can be controlled, and this issue is now being addressed once again in both US and UK trials.[18]

All of this evidence emphasises a number of points: no matter how large a trial in paediatrics more patients would always be better, and this is where carefully controlled meta-analyses can assist interpretation of individual trials; international collaboration, especially involving direct exchange of basic patient data can prove very helpful; and above all the findings from any individual trial must be subject to further scrutiny in the light of changing circumstances with time. Nothing in medicine must ever be assumed to be written in stone forever. Individual paediatric oncologists who have a noble desire to do least harm for their patients may lead to modification of therapeutic protocols, either in the planning stage to avoid short term or even perceived long term risks, or when considering the specific scheduling for an individual patient within a trial. Both of these processes may lead to decreased overall survival for the patient, which is ultimately the worst of all long term sequelae. The reduction of therapy in the early MRC leukaemia trials during the 1970s in order to reduce immunosuppression, is a good example of this phenomenon.[13] Those who challenge the nature of randomised clinical trials claim them to be automatically impersonal, detached, and to take no consideration of the individual patient's needs, whereas in reality there is often a very considerable amount of emotion and of subjectivity associated with both protocol design and its application in any individual patient. Indeed it has become very important to monitor physician and patient compliance with protocols, in order to understand outcome measures for any particular trial.

Subsequent MRC trials in both ALL[16] and acute myeloblastic leukemia (AML)[19] have applied the principles of delivering sustained, intensive therapy for leukaemic patients with continuing improvement in survival. Increasingly in all forms of leukaemia more sophisticated cellular typing (by phenotype, immunophenotype,[20] cytogenetics,[21 22] and molecular genetics) define subsets of patients who on identical therapy appeared to have more or less favourable outcome (for example, favourable features include t(15;17) translocation in AML and probably TEL-AML1 translocation in ALL, while adverse features include monosomy 5 and/or 7 in AML or t(9;22) in ALL). For some of these associations at least, we are beginning to understand mechanisms. For example, the patients with B cell lineage ALL who have high hyperdiploidy (more than 50 chromosomes in their leukaemic cells) have a favourable outcome and they appear to accumulate high concentrations of methotrexate polyglutamates in their lymphoblasts, which appears to enhance cytotoxicity.[22] Statisticians have rightly argued that more intensive treatment appears to benefit all risk groups, albeit to a variable degree.[13 14 16 18] Such a blanket approach may mask specific biological characteristics which warrant totally different approaches. We are only beginning to understand how we should deal with them. The most dramatic improvement applies to mature B cell ALL. Over the last 10–15 years, five year event free survival has gone from zero to 80–85%, with the cessation of treatment using standard ALL therapy and replacement with pulsed cyclophosphamide based lymphoma type treatment.[23]

Similarly both haematological[24] and molecular techniques[25] (using the polymerase chain reaction to amplify clonal rearrangements, for example of T cell receptor and immunoglobulin heavy chain genes) are being used to define the speed of response to therapy in ALL. Slow responders who appear to require more or different therapy are being identified. However, to date no randomised trial has been conducted between therapeutic modalities for such slow responders.

Protocols being designed for any paediatric disease should be based on all the evidence which is available internationally, acquired ideally not just by literature search but by direct contact with as many colleagues in the field as possible. Unpublished negative results and even flaws in the conduct of published trials can only be elicited by direct physician to physician contact. In paediatric oncology we have been greatly advantaged by having international colleagues (especially from the American Children's Cancer Study Group), who have been willing to share data and argue the case for specific approaches. Editors should also be much more willing to publish negative results and trialists must report them. When reading narrative reviews or conducting database searches clinicians must also be aware of writer bias, preferential citation of English language papers, and such omission of negative reports.[26] "Studies of unpublished and published reviews have shown no difference in the quality of the trials, regardless of their publication status".[27] We must not assume that negative findings are unimportant.

In a recent series of editorials addressing the role of clinical trials in paediatric oncology the consensus reached was that they were an essential component in the spectrum of progress from phase I drug trials to accepted state of the art management. They may or may not be innovative but certainly confirm or refute physician prejudice or initial impression.[28][29] When a protocol is being prepared the trial coordinators must ensure that the research question(s) is unambiguous, the methodology to test it exemplary, and that selection criteria are as inclusive as possible, with exclusions minimised. Those reading trial reports should look for evidence of these features and search for evidence of scrupulous randomisation procedures. The Cochrane collaboration not only provides a register of such randomised trials (218 355 reports in its library), but also advice on methodology for systematic reviews and trial scrutiny.[30] It stresses that a greater percentage of any test population entered into a trial always enhances its power and makes its results more generally applicable. For systematic reviews the need for the research questions being addressed to be unambiguous at the protocol stage and for all of the rules regarding search strategy to be clearly defined has recently been emphasised.[31]

We have indeed been lucky in paediatric oncology to be able to work cooperatively using protocols and ask questions within trials. Our adult colleagues have been less able to apply such approaches uniformly, in view of the wide age range with whom they work, and of course other health related aspects including tolerance of therapy. Paediatricians in other subspecialties have had some similar problems. An approach advocated by Charlton *et al*, using what they term PACE (population adjusted clinical epidemiology), appears to be worthy of consideration.[32] Using this technique those in the adult population who can be entered into randomised controlled trials are entered, but the whole population with a particular problem is registered, documented, and treated on standard treatments, which frequently evolve into trials. This approach has worked very effectively in the UK northern region for adult cancer sufferers. Such regional, even national approaches may be the way ahead in other specialties. Stiller and Eatock recently reanalysed survival in the more modern era for children with acute lymphoblastic leukaemia. In the time period 1990–94, ALL survival rates of 84% for patients within trials and 68% for those not in trials were reported.[15] There did not appear to be an association with place of treatment. It is this evidence which suggests a strong survival benefit for those treated on trial protocols, for whatever reasons, which makes paediatric oncologists very keen to continue their approach.

However we approach the accumulation of real evidence in support of specific therapy, and whatever the critics say, evidence based medicine is undoubtedly here to stay. We do owe it to our patients to optimise favourable outcomes and minimise toxicity. It might also just help to keep us out of the courts!

TIM EDEN

Academic Department of Paediatric Oncology,
Christie Hospital NHS Trust,
Wilmslow Road, Manchester M20 4BX, UK
email: alexisdinsmor@christie.tr.n.westnhs.uk

1 Medical Research Council Patulin Clinical Trials Committee. Clinical trials of patulin in the common cold. *Lancet* 1944;**ii**:373–5.
2 Medical Research Council Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;**ii**:769–83.
3 D'Arcy Hart P. A change in scientific approach: from alternation to randomised allocation in clinical trials in the 1940s. *BMJ* 1999;**319**:572–3.
4 Bradford Hill A. Memories of the British streptomycin trial in tuberculosis. *Control Clin Trials* 1990;**11**:77–90.
5 Godlee F, Smith R, Goldmann D. Clinical evidence [editorial]. *BMJ* 1999;**318**:1570–1.
6 Charman C on behalf of Clinical Evidence. Clinical Evidence—atopic eczema. *BMJ* 1999;**318**:1600–4.
7 Ghasziou P, Guyatt GH, Dans AL, Dans LF, Straus S, Sackett DL. Applying the results of trials and systematic reviews to individual patients. *Evidence Based Medicine* 1998;**3**:165–6.
8 Goodman NW. Who will challenge evidence based medicine? *J R Coll Physicians Lond* 1999;**33**:249–51.
9 Anon. Meta-analysis under scrutiny. *Lancet* 1997;**350**:675.
10 Parmar MKB, Stewart LA, Altman DG. Meta-analyses of randomised trials: when the whole is more than just the sum of the parts. *Br J Cancer* 1996;**74**:496–501.
11 Kleinert S. Rationing of health care—how should it be done? *Lancet* 1998;**352**:1244.
12 Sniderman AD. Clinical trials, consensus conferences and clinical practice. *Lancet* 1999;**354**:327–30.
13 Peto J, Eden OB, Lilleyman J, Richards S. Improvement in treatment for children with acute lymphoblastic leukaemia in the Medical Research Council UKALL Trials 1972–84. *Lancet* 1986;**8**:408–11.
14 Eden OB, Lilleyman JS, Richards S, Shaw MP, Peto J on behalf of the MRC Childhood Leukaemia Working Party. Results of the Medical Research Council Leukaemia Trial UKALLVIII. *Br J Haematol* 1991;**78**:187–96.
15 Stiller CA, Eatock EM. Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1984. *Arch Dis Child* 1999;**81**:202–8.
16 Chessells JM, Bailey C, Richards SM on behalf of the MRC Working Party on Childhood Leukaemia. Intensification of treatment and survival in all children with lymphoblastic leukaemia: results of UK MRC Trial UKALLX. *Lancet* 1995;**345**:143–8.
17 Keengwe IN, Stansfield F, Eden OB, Nelhans ND, Dearlove OR, Sharples A. Paediatric oncology and intensive care treatments: changing trends. *Arch Dis Child* 1999;**8**:553–5.
18 Childhood ALL Collaborative Group. Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. *Lancet* 1996;**347**:1783–8.
19 Hann IM, Stevens RF, Goldstone AH, Rees JKH, Wheatley K, Gray RG, Burnett AK. Randomised comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukaemia. Results of the Medical Research Council's 10th AML Trial (MRC AML10). *Blood* 1997;**89**:2311–18.
20 Hann IM, Richards SM, Eden OB, Hill FGH. Analysis of the immunophenotype of children treated on the Medical Research Council United Kingdom ALL Trial XI. *Leukaemia* 1998;**12**:1249–55.
21 Chessells JM, Swainsbury GJ, Reeves B, Bailey CC, Richards S on behalf of the MRC Childhood Working Party. Cytogenetics and prognosis in childhood ALL. *Br J Haematol* 1997;**99**:93–100.
22 Whitehead VM, Vuchich MJ, Lhauer SJ, *et al*. Accumulation of high levels of methotrexate polyglutamates in lymphoblasts from children and hyperdiploid (>50 chromosomes) B-lineage ALL. A Pediatric Oncology Group Study. *Blood* 1992;**80**:1316.
23 Patte C, Philip T, Rodary C, *et al*. High survival rate in advanced stage B cell lymphomas and leukaemias without CNS involvement with a short intensive polychemotherapy protocol. Results from the Rench Pediatric Oncology Society of a randomised trial of 216 children. *J Clin Oncol* 1991;**9**:123–32.
24 Reiter A, Schrappe M, Ludwig WD, *et al*. Chemotherapy in 998 unselected childhood acute lymphoblastic leukaemic patients. Results and conclusions of the multicentre trial AL-BFM 86. *Blood* 1994;**84**:3122–33.
25 Biondi A, Yokota S, Hanset-Hagge TE, *et al*. Minimal residual disease in childhood acute lymphoblastic leukaemia: analysis of patients in continuous complete remission or with consecutive relapse. *Leukaemia* 1992;**6**:282–8.
26 Coursol J. Effect of positive findings on submission and acceptance rates: a note on meta-analyses bias. *Professional Psychology* 1986;**17**:136–7.
27 Williams C. Evidence-based medicine angling out his helix. *Amgen's Magazine of Biotechnology* 1999;(2):23–8.
28 D'Angio GJ. Cancer controversies. Clinical trials confirm but don't innovate—pro. *Med Pediatr Oncol* 1998;**31**:525–6.
29 Girling DJ. Cancer controversies. Clinical trials confirm but don't innovate—con. *Med Pediatr Oncol* 1998;**31**:522–4.
30 Cochrane Collaboration Library and Cochrane Cancer Network. www.cochrane.co.uk and www.canet.demon.co.uk.
31 Eysenbach G. Research questions for systematic reviews must be unambiguous from protocol stage [letter]. *BMJ* 1999;**318**:1265.
32 Charlton BG, Taylor PRA, Proctor SJ. The PACE (population-adjusted clinical epidemiology) strategy: a new approach to multi-centred clinical research. *QJM* 1997;**90**:147–51.