CORRESPONDENCE

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Tribulations for clinical trials

SIR,—Mr I M C Macintyre highlights a growing problem in clinical research.[1] We are actively involved with various trials and would like to share several points based on our own experience.

If a common reason for doctors' failure to enter patients into randomised trials is their reluctance to admit uncertainty about what is the "best" treatment then adopting an honest approach should improve recruitment. Patients can better appreciate the point of a study and be more amenable if approached for consent by someone who can truly profess not to know which treatment is best. Extending the argument, clinicians who are asked to help conduct randomised trials should not commit themselves if they think that they already know the "best" treatment because they will be unable to obtain consent from patients without a clear conscience and their enthusiasm for recruitment will be lacking.

Mr Macintyre also alludes to medicosocial changes hampering recruitment. We would argue that this applies largely to the sort of clinical trials that persist in imposing irrelevant study criteria and clinically unrealistic interventions (thereby producing results of limited if not dubious practical application) as well as unnecessary tests. Such studies become trials of patient compliance for the patient and exasperate the overworked researcher. There may be an inverse relation between the number of recruits achieved and the inconvenient complexity of any study and amount of paperwork involved—both often reflected in the bulk of the case record form.

Finally, we think that patients who help out in trials for altruistic reasons are a dwindling breed. Increasingly, we find it necessary to persuade potential recruits that they stand to benefit directly from participation, and the more obvious the benefits the more readily is consent given. In trials related to ischaemic heart disease, for example, recruitment is facilitated when requisite tests or interventions that are also clinically indicated can be proferred as a "package deal." Patients like the incentive of the certainty of timing of various procedures that comes with participation in trials, and trial designers should also take note of usual time frames for such interventions in proposed participating centres. Just as it would be unethical to delay clinically indicated interventions so that the study could be completed, it would be equally unacceptable in our view to obtain consent from patients for trials where incompatible time scales may curtail continuing participation.

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1 Macintyre IMC. Tribulations for clinical trials. *BMJ* 1991;**302**: 1099-100. (11 May.)

SIR,—The difficulties outlined by Mr I M C Macintyre[1] accord with my own working in another field where there are, in addition, somewhat different problems relating to recommendations about the design of clinical trials.

The recent development of potentially effective pharmacological agents for treating Alzheimer's disease has led to the growth of trials relating to this condition. Patients in the early stages of the condition and their relatives are prepared—indeed, eager—to volunteer for clinical trials which provide the faintest hope of receiving potentially effective therapy, but they are understandably reluctant to take a placebo unless assured that at some stage they may receive the putatively active preparation. The obvious solution would be to elect for a crossover design with an adequate wash out period so that all patients entering the trial are assured of receiving the "active" preparation at some stage.

The current view of many experts on trial design does not, however, favour this approach, and there are increasingly strong recommendations for the adoption of parallel group designs; these are considered best in a condition where gradual deterioration is the rule. It is agreed that the deterioration produces a shifting baseline, which makes crossover trials difficult to analyse. This purist approach is embodied in the draft guidelines for the clinical evaluation of antidementia drugs drawn up by the Food and Drug Administration in November 1990 and looked upon with some favour by European authorities. In view of the potential size of the American market these are likely to be adopted by firms and research organisations based in the United Kingdom. It can be argued that there are perfectly acceptable statistical methods of dealing with shifting baselines and that these should be adopted rather than compounding the problems of obtaining subjects for clinical trials in dementia by always enforcing parallel group designs.

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1 Macintyre IMC. Tribulations for clinical trials. *BMJ* 1991;**302**: 1099-100. (11 May.)

SIR,—As coordinator at the Scottish Cancer Trials Office in Edinburgh I read Mr I M C Macintyre's editorial with interest.[1]

In 1982-3 we started a pilot study to see whether a multicentre trial, comparing mastectomy with breast conserving therapy in patients with operable breast cancer, would be viable. This idea was abandoned as only 16 (21%) of the first 78 women referred accepted randomisation, the remainder having a strong preference for one or other form of treatment.[2] In other words, the problem of recruitment was greater than that of the study referred to by Mr Macintyre.

The reference to the Scottish breast cancer trial, to which "fewer than half the eligible patients could be recruited" is in fact to a study of the referral pattern from a single unit during 1988 and to a trial in which patients who have had breast conserving surgery are randomised for immediate postoperative radiotherapy or observation.[3] It can only be assumed that the findings are applicable to the trial as a whole. It is of interest, however, to note that of the 103 patients who were suitable for conservation, 19 (18%) were not randomised because of a preference for mastectomy; this is only a small reduction from the finding in the 1982 series of 18/78 (23%).

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1 Macintyre IMC. Tribulations for clinical trials. *BMJ* 1991;**302**: 1099-100. (11 May.)
2 Stewart HJ, Robinson SM. Recruitment to breast cancer trials. *Lancet* 1984;ii:1096-7.
3 Jack WJL, Chetty U, Rodger A. Recruitment to a prospective breast conservation trial: why are so few patients randomised? *BMJ* 1990;**301**:83-5.

Randomised controlled clinical trials

SIR,—There have been some misunderstandings about the introduction, by the Medical Research Council, of randomised controlled clinical trials of treatment. Since the central role of their Tuberculosis Research Unit has become obscured or even—as shown in the obituaries of Sir Austin Bradford Hill[1,2]—ignored, may I record the sequence of events as I recollect them?

In 1946, because indiscriminate use in the United States of the new antituberculosis antibiotic streptomycin made its proper evaluation impracticable, the Medical Research Council decided to assess its efficacy scientifically. The council created the Tuberculosis Research Unit specifically for this purpose (with myself as director and Marc Daniels as my deputy), and a special MRC committee (chairman, Sir Geoffrey Marshall; secretary, myself) was set up to guide the research. In his memories of the first British trial of streptomycin in the treatment of pulmonary tuberculosis, Sir Austin Bradford Hill (who was then director of the MRC Statistical Research Unit and the statistician on the committee) told of the thinking behind this historic trial.[4]

He had recently advised the use of random sampling numbers in the second MRC prevention trial of vaccination against pertussis (started in 1946 and reported in 1951) but "I had not, up to this point, had an opportunity to use treatment assignment by random sampling numbers in the clinical situation. Now the occasion arose and I was, therefore, completely ready for it." He then refers to the Tuberculosis Research Unit: "D'Arcy Hart . . . had been frustrated, I think, by some

15 years of using and reading reports on treatment with gold without being able to make a controlled trial to find out whether it really was effective or not. So I think that he himself, if something new came along and there was a chance of making a really good controlled trial, was ready to seize that opportunity.[5] He argued from the medical point of view while I was arguing from the statistical."

I must add that I had come to this project much influenced by the techniques of an earlier (and largely forgotten) double blind controlled trial of the treatment of the common cold with the antibiotic patulin, in which a random assignment to patulin or a control solution had been achieved by an effective alternation scheme.[6] This trial was guided by a special MRC committee (chairman, Sir Harold Himsworth; statisticians, Professor Major Greenwood and Dr W J Martin; secretary, myself; coordinator, Dr Joan Faulkner); it started in 1943 and was reported in 1944.[6] Thus, medical and statistical disciplines converged at the initiation of the first MRC streptomycin trial.

The design was jointly by Bradford Hill, Daniels, and myself; the trial started in 1947 and the first report was in 1948.[7] "It ushered in the new era of medicine."[4] The council's report for 1948-50 remarks: "The experience gave the TRU the opportunity to improve the statistical design and analysis of controlled trials." This the Tuberculosis Research Unit (and its successor the MRC Tuberculosis and Chest Diseases Unit (1965-86), directed by Dr Wallace Fox) did in numerous subsequent trials, with the cooperation for more than 10 years of Dr Ian Sutherland, then a member of the MRC Statistical Research Unit.

One of the most notable trials (started in 1956) was from the Madras Chemotherapy Centre (under WHO, the Indian government, the Madras state government, and the MRC); it was established and directed by Wallace Fox for the Tuberculosis Research Unit, with Professor D A Mitchison (director of the MRC Unit for Research on Drug Sensitivity in Tuberculosis) responsible for designing the crucial laboratory studies. In this trial the methodology was further developed to show that admission to hospital was unnecessary for the successful drug treatment of tuberculous patients and for the protection of their contacts. Later, short term chemotherapy was devised and tested successfully in outpatients. These observations had worldwide impact and led to radical changes in the management of tuberculosis. Another notable trial (1950-70) was of tuberculosis vaccines (mainly BCG), which showed considerable and durable protection in the United Kingdom.

Thus, the MRC Tuberculosis Research Unit and its successor, during four decades, introduced and refined the techniques of the randomised controlled clinical trial. I have not here considered the many problems that had to be overcome in the unit's practical implementation of the trial designs to ensure meaningful advances in treatment and prevention of tuberculosis.

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1 Anonymous. Sir Austin Bradford Hill (obituary). *BMJ* 1991; **302**:1017. (27 April.)
2 Anonymous. Sir Austin Bradford Hill. *Daily Telegraph* 1991 April 23:17.
3 Godber G. Vital statistics. *Guardian* 1991 April 23:37.
4 Hill AB. Memories of the British streptomycin trial in tuberculosis. *Controlled Clinical Trials* 1990;**11**:77-90.
5 Hart PD'A. Chemotherapy of tuberculosis: research during the past 100 years. *BMJ* 1946;ii:805-10,849-55.
6 MRC Patulin Clinical Trials Committee. *Lancet* 1944;ii:373.
7 Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;ii:769-83.

Controversy breeds ignorance

SIR,—The recent account of the experience of a couple whose baby, Adam, was thought to be at risk of toxoplasmosis was both moving and salutary.[1] It is important that we draw the right lessons from their experience.

The author suggests that only the institution of a screening programme for toxoplasma infection in pregnancy could dispel the ignorance that led to this tragedy. There are, however, strong scientific arguments against screening. These arguments have been rehearsed in a recent editorial in the *Lancet*.[2] In summary, toxoplasma infection in pregnancy does not fulfil the standard criteria for a screening programme. Unlike the situation in France, where a screening programme does exist, congenital toxoplasmosis seems to be uncommon in the United Kingdom, and the low seroprevalence in women (20% *v* 80% in France) would necessitate obtaining repeated blood samples from 80% of women throughout pregnancy. In addition, there remains doubt about the clinical course of untreated congenital toxoplasmosis, about the efficacy of treatment, and, as a result of individual variability in the persistence of IgM, about the reliability with which serological tests can distinguish between infection acquired early in pregnancy and that acquired before conception. With the tests and techniques now available there is a strong possibility that more women would experience unnecessary trauma and intervention than would benefit from a screening programme.

The real lesson is the need for better dissemination of information about the management of this and other congenital infections. This was an entirely preventable tragedy: there is no evidence that there is any risk of congenital toxoplasmosis infection in a fetus conceived at least seven months after an acute infection. Persistence of antibody does not imply active infection and there is therefore no rationale for the use of spiramycin nor for cordocentesis in this situation.

Toxoplasmosis is not the only infection in pregnancy that has the potential for mismanagement leading to disastrous consequences. We have accumulated several case histories from women who have been exposed to possible rubella in pregnancy and whose medical advisors seemed not to know how to proceed.

Although congenital infections are uncommon, infections in pregnancy are not. We suggest that every obstetric unit should produce a simple policy guide for the management of women who have acquired, or been exposed to, infections in pregnancy. In most circumstances this will consist of appropriate reassurance that their infant is not at risk. Where there is a possibility that the fetus might be damaged the necessary investigations can then be carried out quickly, an assessment of risk made, and the parents appropriately counselled.

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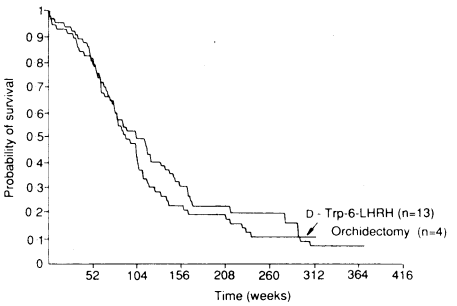
1 Anonymous. Controversy breeds ignorance. *BMJ* 1991;**302**: 973-4. (20 April.)
2 Anonymous. Antenatal screening for toxoplasmosis in the UK [editorial]. *Lancet* 1990;**336**:346-8.

Medical or surgical orchidectomy?

SIR,—In their short report Mr D J Chadwick and colleagues state that there is little evidence to indicate whether patients with prostatic cancer prefer medical or surgical castration when they are offered the choice.[1] Furthermore, they state that no such study has been carried out in the United Kingdom. Neither statement is correct.

In 1985 we reported the results of a prospective randomised clinical trial comparing D-Trp-6-luteinising hormone releasing hormone with surgical orchidectomy.[2-4] Fifty five patients were randomised to receive the hormone and 49 to have orchidectomy. The trial incorporated a cross validated psychological questionnaire to assess both response and psychological wellbeing after medical or surgical orchidectomy. Although there was no statistical difference between the two groups, there was a trend, in that patients given the hormone tended to have less fatigue, anger, composure, depression, and anxiety and were more cheerful and energetic than the orchidectomy group at six months. As all of our patients were aware of the diagnosis the psychological impact of the cancer seemed to override the immediate impact of surgical orchidectomy. Perhaps having more patients in the trial might have given a statistically significant result.



Probability of survival at six years among 65 patients given D-Trp-6-luteinising hormone releasing hormone (D-Trp-6-LHRH) and 57 who had orchidectomy

In a letter in the *BMJ*[1] we gave follow up data concerning the preference of the patients. When the patients were told about the equivalent clinical results of surgical and medical orchidectomy 70% of those who had had surgical orchidectomy stated that they would select medical treatment if given a choice; all the patients taking D-Trp-6-luteinising hormone releasing hormone preferred to continue receiving the drug as long as they were in remission.

We recently analysed the survival of all the patients entered into the trial. Altogether 122 patients were entered: 65 received D-Trp-6-luteinising hormone releasing hormone, of whom 52 have died, and 57 had orchidectomy, of whom 53 have died. The median survival was 91 weeks (range 1-371 weeks) in the orchidectomy group and 102 weeks (2-315 weeks) in the group given the hormone. The probability of survival at six years for the orchidectomy group is 0·07 and for the group given the hormone 0·10 (figure). These figures are not statistically significant but indicate that long term survival is possible and easily achieved with a simple injection once a month without any appreciable long term side effects.

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1 Chadwick DJ, Gillatt DA, Gingell JC. Medical or surgical orchidectomy: the patients' choice. *BMJ* 1991;**302**:572. (9 March.)
2 Parmar H, Phillips RH, Lightman SL, Edwards L, Allen L, Schally AV. Randomised controlled study of orchidectomy vs long-acting D-Trp-6-LHRH microcapsules in advanced prostatic carcinoma. *Lancet* 1985;ii:1201-5.
3 Parmar H, Edwards L, Phillips RH, Allen L, Lightman SL. Orchidectomy versus long-acting D-Trp-6-LHRH in advanced prostatic cancer. *Br J Urol* 1987;**59**:248-54.
4 Parmar H, Phillips RH, Edwards L, Partridge SE, Lightman SL. Treatment of prostatic cancer. *BMJ* 1988;**296**:1001-2.

Emergency contraception

SIR,—We commend Dr F C Reader's editorial encouraging professionals and the public to think of postcoital contraception as emergency contraception that can be administered beyond the "morning after."[1]

We believe, however, that her recommendation