pointed out that tunnelling might reduce the infection rate when nursing care was inconsistent or substandard. Special intravenous therapy teams for insertion of most and maintenance care of all catheters have been advocated, mostly by American workers, and undoubtedly results can improve with committed personnel. Whilst the services of such a team are unlikely to be available in UK hospitals their emphasis on the principles of rigorous aseptic techniques and frequent observation of the catheter site together with removal of infected or non-functioning catheters must not be forgotten.

Each infection of an intravenous catheter reflects a failure of aseptic technique and as such should be preventable. It is to this end that efforts should be directed and not to the treatment of established infection. Although in many patients removal of the catheter alone will cure the associated infection, antibiotics are frequently given at the same time and are sometimes clearly justified particularly if another catheter is required since this too can rapidly become infected with the same organism. The choice of antibiotic will be governed by the sensitivity or likely sensitivity of the organism isolated from skin site, catheter tip or blood. In the absence of available information a 'best guess' should take account not only of organisms recently isolated from other sites, particularly the sputum, but also of previous or current antibiotic therapy. Whilst the sensitivity of Staph. aureus is reasonably predictable, that for Staph. epidermidis is far less so and multiply-resistant strains are becoming the norm. At present vancomycin is one of the few antibiotics to which Staph. epidermidis is always sensitive and it is the antibiotic of choice in the absence of sensitivity data. It is seldom necessary to treat these infections for more than a few days and as with the treatment of so many bacterial infections it is preferable to tailor the therapy to the individual, monitored by the clinical response, than to be bound by rigid dogma.

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Quality of antibiotic clinical trials
In the ideal clinical drug study, a well-defined disease is treated, and the drug is compared to placebo or an active control using a double-blind design. To evaluate therapeutic efficacy a continuous variable such as blood pressure, blood glucose or heart rate is used. Such a study performed in a limited number of patients can still yield statistically reliable results. But when antibiotics are evaluated for clinical and bacteriological efficacy, one does not have continuous variables; the infections treated may vary with respect to causative organisms and site of infection, and the infection itself is often not an isolated phenomenon but rather the consequence of an underlying condition, which in itself may affect the outcome. These and many other factors seem to have led a certain amount of resignation among investigators performing clinical trials on antibiotics, and as a consequence a high proportion are of poor quality. At this stage it should be mentioned that all critical remarks in this article on the quality of antibiotic trials could be exemplified from the published trials of which I am the author.

Ethical considerations
As recommended in the Declaration of Helsinki, every biomedical research project involving human subjects should be submitted to an independent committee for consideration, comment and guidance. To be able to carry out its function well the committee must be highly competent. In 1981 Baum et al. reviewed published articles in which antibiotic prophylaxis for patients undergoing colo-rectal surgery had been compared with placebo or no treatment.
They found that although it was proven in 1970 that antibiotics reduce morbidity and in 1975 that they reduce mortality, 14 studies using placebo or no treatment as controls were initiated after 1975. The blame for that rests of course mainly with the investigators but the review committees should have stopped the studies. In addition to reviewing the precedent for the trial, the committee should consider the risk to the patient. Since no clinical trial is completely without risk, it must be designed in such a way that the objectives defined in the trial protocol can be met. If that is not the case it seems reasonable to suggest that a basic principle of the Declaration of Helsinki is not fulfilled and that the trial should not be started.

Controlled or uncontrolled studies?

In Volume 12, 1983 of this journal, ten clinical trials were published. One was a retrospective uncontrolled trial, five were prospective and uncontrolled, one was prospective, controlled and non-randomized while three were prospective, controlled and randomized. In the latter studies it was not stated whether the randomization was blind or not. In none of the studies was a blind design used. These characteristics are not different from any other journal publishing clinical trials of antibiotics, and they are not to be seen as a specific criticism of this journal. However, they indicate that the requirements for antibiotic studies are less strict than for many other drugs.

It seems clear that few if any conclusions can be drawn from an uncontrolled study. Even in those that are controlled it has been shown that unless the randomization is blind, for instance using sealed envelopes, the prognostic variables and the outcome of treatment tend to favour the treatment in comparison to the control (Chalmers et al., 1983). A study should be double-blind whenever possible: situations in which open designs must be considered are those where dosage of one of the components (as with aminoglycosides for instance) has to be adjusted during treatment. In such a case the use of a blinded evaluator or a single-blind design should be considered.

Trial size

Antibiotic studies require very large numbers of patients, partly because continuous variables cannot be used, and partly because placebo or no-treatment controls are often unethical. One is therefore faced with a situation in which an attempt has to be made to prove equal efficacy or superior safety. The latter can often be done with reasonably small patient numbers, while efficacy studies require very large groups. Two statistical errors, type I and II, have to be considered. The type I error is the statistical possibility that a null-hypothesis is falsely rejected and is expressed as a significant p-value. Arbitrarily P<0.05 is considered statistically significant in most studies. No-one has so far been able to explain why P=0.051 is not statistically significant while P=0.049 is significant. Most investigators feel acquainted with the type I error but less so with the type II error, which means the statistical possibility that a null-hypothesis is falsely accepted, i.e. that a statement of no difference is not true. In an analysis of 71 trials in which a statement of no difference was made, Freiman et al. (1978) showed that in 50 of the studies there was a greater than 10% risk that a 50% difference between the two regimens studied could have been missed due to insufficient sample size. Using a type II error of 0.2, i.e. a 20% or less risk (power of 80%) that a true difference is not detected, and assuming that a new drug will not differ from a control drug with 80% efficacy by more than 10%-units, about 200 patients will have to be entered into each study group. It is obvious that few centres are of a size to enable an investigator to recruit 400 patients for a clinical study. Therefore it is often necessary to pool data from more than one investigator in order to achieve a statistically meaningful patient population. In turn, this means that a multiple independent trial (MIT) or multicentre trial (MCT) design will have to be used, as discussed below.

Inclusion and exclusion criteria

The results of a perfect antibiotic study should have a high external validity; that is the results should be valid for many patients with the type of infection treated. This target can be met only by the use of wide inclusion criteria and few exclusion criteria. If, for example, only patients aged up to 65 years are included, the results cannot be extrapolated to patients above that age, which is the age when infections commonly occur. When criteria have been established, it is important in all trials that their effects on patient eligibility be evaluated. The investigator may find that only a few patients with a certain type
of infection will be eligible for the study, but ideally, consecutive patients should be entered. This means that all patients who are assessed but not entered into the study should be listed in a reject log, which gives the reason for not entering the patient into the study.

One thing often overlooked is that patients with infections caused by an organism resistant to one of the antibiotic regimens studied must be excluded from full evaluable. If this is not done, the outcome of a study can be decided beforehand by choosing a suitable comparative agent with gaps in its antibacterial spectrum that are covered by the test drug.

**Registration and evaluation of efficacy and safety**

All end-points for efficacy and safety should be defined and described beforehand in the trial protocol. The antibiotic trials dealt with here are ‘management’ trials, and the ‘intervention-to-treat’ principle applies, meaning that the trials aim at evaluating the clinical results of treatment. As a consequence all patients who are randomized must be evaluated for safety and efficacy although some patients will not fulfil all criteria; they may not have identified aetiology, they may have dropped out due to adverse reactions or they may have withdrawn from the study prematurely. At the end of the study there will be one group of patients who received treatment for a sufficient time and who had aetiology verified infections that were adequately followed up, and there will be one or more groups in which these requirements are not fulfilled. In deciding the trial size, the frequency of patients who will not be fully evaluable must be estimated. In a study of treatment of serious systemic infection, about 25% of all patients will have infections of undefined aetiology. In treatment of febrile episodes in granulocytopenic patients this will be the case for about 70% of patients (EORTC International Therapy Project Group, 1978). A way in which many investigators have tried to solve this problem is by multiple entry, where a patient who has been treated in the study once and who subsequently develops a new infection is allowed to re-enter. This is very difficult to justify statistically and should be avoided.

In the evaluation of safety of an antibiotic, the rule that ‘one finds what one is looking for’ applies. Preferably, the registration of adverse events should be both passive and active; the patient is first asked if he or she has experienced anything during treatment which could be due to the treatment, and subsequently interviewed specifically about symptoms known to occur as adverse reactions to the drugs used. Obviously the result obtained with the two techniques will be different, and while the passive technique is likely to under-estimate the true frequency of adverse reactions, the latter will give information that to a certain extent is non-relevant. However, if the study is controlled, reactions that are more common with one trial drug will be detected.

**Multiple independent trials (MIT) and multicentre trials (MCT)**

For reasons discussed above it is often impossible to achieve sufficiently large numbers of patients in a single centre study. By the use of data from several centres there are two possible ways of increasing numbers of patients. With the MIT design, several investigators do their trials independently from each other but with a trial protocol that is similar in all important respects. The studies may be started at different times and the data will finally be pooled, usually by the manufacturer. Ideally, each investigator in an MIT should have a sub-project, for example a pharmacokinetic or a microbiological study, which will allow separate publication. Investigators should be made aware of the fact that their data will be used in an MIT.

The MCT involves more complicated coordination of those participating. Each centre must start the study at the same time and perform it according to an identical routine. The co-ordination process is costly and the credit to the participants is minimal in relation to the work put into the study. However, it is possible to include individual sub-projects if they do not disturb the main project and in the end the results of an MCT are often of a quality that justify the efforts made.

As with a more extensive recent review of the subject (Norrby, 1984) the intention of this article is not to discourage investigators from performing antibiotic clinical trials, but rather to create an awareness of the need for education in their design and to encourage discussion of these problems. Organizations such as The British Society for Antimicrobial Chemotherapy could consider this field. There may be a role, for instance, in devel-
Leading articles

oping guidelines for hospital ethical committees. After all the ultimate test of an antibiotic is whether or not it works in patients.

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