the possibility to prevent mucosal damage, in order to reduce portals of entry for the streptococci and prevent systemic infection.

Several studies have demonstrated that sucralfate might afford protection for the oral and gastric mucosa, and preliminary studies suggest also that epidermal growth factor might be useful for the prevention and treatment of cytotoxic mucosal lesions. The use of the soft laser at the Centre Antoine-Lacassagne in Nice for both preventive and curative purposes has given encouraging results for chemotherapy-induced mucositis as have various topical ointments. However, controlled trials have yet to be performed with all these various approaches to prevent mucositis and subsequent streptococcal infection in neutropenic patients.

Herpes infections also appear to be potentially responsible for streptococcal sepsis in neutropenic patients; streptococci adhere well to herpes-infected cells, and prior incubation of these cells with an antiherpes antibody prevents bacterial adherence. Preliminary studies suggest that streptococcal septicaemias have nearly disappeared since the introduction of acyclovir for prophylactic purposes in transplant recipients [3]. These findings must, however, be confirmed by prospective studies. The avoidance of chemotherapy regimens known to alter profoundly the digestive tract mucosa might also help to reduce the frequency of streptococcal infections.

Given the low mortality rates reported for streptococcal bacteraemias, many clinicians feel that these infections are relatively trivial and that empirical prescription of a glycopeptide to a neutropenic patient presenting fever is not as mandatory as the coverage of gram negative sepsis. As already mentioned, the mortality rate for streptococcal septicaemia might actually be close to 15%; moreover, overall morbidity is considerable especially when serious complications, such as adult respiratory distress syndrome, occur.

The accepted empiric approach today, in febrile granulocytopenic patients, is the administration of a third-generation cephalosporin, with or without an aminoglycoside, with vancomycin being prescribed only for microbiologically proven gram positive infections [4]. An alternative might be a full coverage from the start; in other words, a cephalosporin (with or without an aminoglycoside) plus a glycopeptide, with prompt discontinuation of some of these components as a function of the microbiological and clinical results. So far, several studies have indicated an advantage of early empiric administration of vancomycin to febrile neutropenic patients in terms of clinical response [5–7].

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Patients Excluded from Entry to Clinical Trials

MOST PATIENTS are not entered into a clinical trial, either because the treating clinician is not participating in a trial relevant to their disease; because the patient is ineligible for entry to such a study; or, despite being eligible, the patient is not entered for a number of reasons.

Langley *et al.* [1] interviewed 52 clinical oncologists, including all available radiation and medical oncologists at two large cancer treatment centres in Toronto. During the interview, a questionnaire was completed in which the oncologists were asked to rank the factors that affected the decision to offer or not to offer trial entry to patients, and to specifically enquire about the relative importance of three variables, *viz.*, the scientific design of the study, the effect on doctor–patient rapport, and the ease of obtaining informed consent. Of 51 oncologists who completed the relevant section of the questionnaire, 47 (92%) ranked the scientific design as being the most important factor in determining their decision whether or not to participate in a trial. Only 3 (6%) put doctor–patient rapport first, and just 1 (2%) ranked difficulty in obtaining informed consent as being the most important factor. This study did not focus on a particular clinical trial, of course, and in this context the oncologists felt that the scientific quality and importance of the question being asked was the most important determinant of their decision about participation in a trial.

Taylor *et al.* [2] considered the rather different question as to why clinicians did not enter all eligible patients into a trial in which they were participating—the US National Surgical

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Adjuvant Project for Breast and Bowel Cancers (NSABP) trial begun in 1976 to compare segmental mastectomy with postoperative radiotherapy with segmental mastectomy alone. Here, the results were quite different, but, as all the respondents were participants in the trial, the question of the scientific quality and importance of the study had already been answered to their satisfaction. Of 66 respondents, the most common reason given (by 48 of 66, 73%) for non-entry of an eligible patient was concern about the doctor–patient relationship. In addition, 25 (38%) mentioned trouble with obtaining informed consent, and 15 (23%) disliked open discussion about uncertainty. Of course, this was a US study, and the nature and extent of the information given to patients will have presented a greater problem than in most other countries.

The third reason for non-entry of patients into a clinical trial is ineligibility, as judged by the study's inclusion/exclusion criteria. Recently, in this Journal, Fentiman *et al.* [3] set out the reasons for non-entry into EORTC trial 10853 of 139 (64%) of 216 patients with biopsy-confirmed ductal carcinoma *in situ* (DCIS) identified in 6 centres between 1985 and 1989. The principal reasons for exclusion were that the DCIS was too extensive (76 of 139, 55%) or that the patient had had a previous breast cancer (25 of 139, 18%). Only 6 (4%) of the patients refused to take part in the trial. The authors commented that the eventual results of the trial may be applicable only to a minority of patients with DCIS, only 77 (36%) of the 216 patients having been entered into the trial.

It has been strongly argued [4–6] that cancer clinical trials do not need to have rigorous entry criteria and that patient heterogeneity enables the importance of prognostic factors to be assessed. As well as having limited generalisability, a study with strict inclusion/exclusion criterial will have difficulty in recruiting a sufficient number of patients to have adequate power of detecting clinically important differences between treatment and to give a reasonably precise estimate of the likely difference between the treatments. Refusal to consent to being entered into the trial must, of course, be respected. Other reasons for exclusion require careful consideration. For example, it may be considered that at least one of the treatments is either inadequate or too radical for a certain type of patient, and that the treatment of choice is known, or that a different trial is more relevant to certain patients. That is, the area of uncertainty has been clearly defined and that the excluded patients should be treated in a manner that has been established by previous work or that the uncertainty pertaining to them is different from that being addressed by the study from which they have been excluded.

If, however, strict inclusion/exclusion criteria simply make a trial appear to be scientifically "pure", and the excluded patients are not being used to provide information regarding choice of treatment, a more pragmatic approach [7, 8] should be considered in which a greater proportion of patients can be entered into the trial, or, if this is judged to be impossible, other trials need to be designed to consider the treatment options relevant to such patients.

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