tumour destruction. The elimination of all cells of a particular lineage, whether normal or malignant, could also be a goal. Thus genetic pancreatectomy and bilateral mastectomies might in future be possible as non-invasive procedures.

Another method to manipulate the somatic genetics of cancer *in vivo* is to down-regulate the expression of specific genes using informational drugs. These can act at several levels. Antisense oligonucleotides can block the activation of transcription by binding to promoter regions, and of translation by preventing transport of mRNA to the ribosome. Furthermore, the recent demonstration that oligonucleotides can recognise DNA sequences specifically resulting in a triplex DNA cofiguration which sterically hinders gene expression provides another avenue for gene therapy. Specific ribozymes and proteases could also lead to the effective down-regulation of tumorigenic proteins.

Finally it may be possible to replace defective tumour suppressor genes known to be relevant in a wide range of human cancers. Homologous recombination—the exchange of new genes for old—can work well *in vitro*, but can it be made to work in the complex environment of a bulky and perhaps poorly accessible tumour within a patient? It is more likely that such approaches will be most powerful in the adjuvant setting, relying on surgery, radiotherapy and in some cases chemotherapy to reduce tumour burden as much as possible. Other strategies include increasing the resistance of normal bone marrow cells to high-dose chemotherapy by enhancing their expression of colony stimulating factors or multidrug exporting proteins such as P glycoprotein. Whether this can enhance survival without the risks of an autologous bone marrow transplant remains to be seen.

The ethics of gene therapy for cancer are relatively straightforward despite the endless debate about other potential uses. No attempt is being made to change the germ line so the fear of mutant monsters emerging can be discounted. Perhaps the biggest worry is that of raising our patients' expectations prematurely. The real question is when will the technology, which at the moment does not even work well in tissue culture, be ready for clinical exploitation. Table 1 lists some of the possibilities. It is likely that by the end of decade the human genome will have been completely sequenced giving us a superb database. New flexible vectors will be available for *in vivo* use. We will have a much clearer understanding of the mechanics behind the interaction of DNA, RNA and protein during the control processes of transcription. All this could provide the momentum on which to base novel therapeutic strategies for the next millenium.

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Are We Giving Tamoxifen for Too Long?

THE DEVELOPMENT of anti-oestrogens [1, 2] and the ubiquitous use of tamoxifen to treat selected patients at each stage of breast cancer [3] has provided the practising oncologist with an agent that appears to be safe and effective. However, issues of safety and continuing efficacy need to be addressed and debated so that our concepts and perceptions of an agent can be revised in the light of current clinical experience.

The concept of adjuvant therapy provided the opportunity to cure patients with breast cancer by destroying the micrometastases that were disseminated throughout the body. Naturally, adjuvant cytotoxic chemotherapy was initially selected as the appropriate strategy because of proven efficacy in advanced disease; however, concerns about an unacceptable level of side-effects often resulted in the delivery of suboptimal doses of drugs. In contrast, tamoxifen therapy was known to have a low level of side-effects and some women with advanced disease had been found to receive palliative benefit for about a year. As a result many trials [4, 7] evaluated the benefit of 1 year of adjuvant tamoxifen therapy. This decision was made because tamoxifen could not be expected, based on experience in advanced disease, to provide benefit for the majority if used longer. Indeed the prolonged use of tamoxifen could have lead to premature drug resistance. Nevertheless, laboratory studies [8] were able to provide a rationale to attempt trials of long-term (2–5 years) tamoxifen therapy [9–13]. Although unselected patients, i.e. receptor negative or unknown patients, were entered in the studies, an improvement in disease-free survival and, in fact, survival was eventually observed. This result contrasts with the disappointing performance of 1 year of adjuvant tamoxifen therapy in individual trials to improve survival.

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Most importantly, overview analysis of all randomised trials has confirmed that adjuvant tamoxifen provides survival benefit to node positive postmenopausal women [14]. However, perhaps it is time to evaluate the therapeutic strategy and to comment on the competing mechanisms that will determine the success or failure of the approach in an individual patient.

Tamoxifen is more likely to produce benefit in receptor positive disease than receptor negative disease [3]. Nevertheless, some indirect mechanisms, such as regulation of insulin-like growth factor 1 (IGF-1) [15, 16], might provide benefit in some patients classified as receptor negative by biochemical assay of the primary disease. This is not to say that the tumour tissue is not really hormone dependent. Just because a laboratory cannot measure the oestrogen receptor (ER) level does not mean the ER is not there or was not there before the tumour started on its odyssey to the laboratory, or that ER is not present in the distant micrometastases that remain in the patient. The clinical problem is clearly who to treat for the best advantage and for how long. Regrettably, patient selection in the clinical trials has not been rigourous and as a result competing resistance mechanisms make the evaluation of duration of therapy difficult. A homogeneous patient population with functional ER (up to half of clinically determined ER may be vestigial) would need to be recruited to test the hypothesis that indefinite therapy may be superior to 2 years of therapy. Unfortunately, this is not realistic and clues to future strategies need to arise from an examination of existing evidence.

One interesting observation from clinical trials is the lasting benefit observed in patients receiving adjuvant tamoxifen therapy [14]. In the small trials of 1 year of tamoxifen this is seen only as an improvement in disease-free survival, but an improvement nevertheless. Clearly tamoxifen is able to alter the natural history of the disease; either early micrometastases are destroyed by preventing angiogenesis or tamoxifen has produced a significant antitumour effect on the overall tumour cell number to aid patient survival. Whether longer tamoxifen therapy will prove to be better, or whether in fact some patients are cured rather than have a delayed recurrence, remains to be determined. It is encouraging that survival is improved in some patients but the benefit for each patient must be weighed against the financial burden of prolonging the therapy.

An obvious defense for prolonging tamoxifen therapy beyond 2–5 years would be to find advantages for the patient over and above controlling breast cancer. A competing cause for death in women in their 60s is coronary heart disease and atherosclerosis. Tamoxifen has a significant level of oestrogenic activity that lowers circulating cholesterol [17] which ultimately may translate into a reduced cardiovascular mortality. Indeed a reduction in cardiovascular mortality in patients with node negative disease might become a primary reason to maintain patients on tamoxifen therapy over and above the modest improvements in disease recurrence [18]. Similar arguments could be made about the potential of tamoxifen to reduce bone loss and retard the development of oesteoporosis in women during their 60s and 70s. However these advantages require proof and the clinical community should be encouraged to address these hypotheses because of the enormous impact on public health if a positive result is established.

Another reason to prolong tamoxifen adjuvant therapy would be to prevent a second primary tumour and avoid the need to perform a second mastectomy. Animal studies have demonstrated the principle [19, 20] and the recent evaluation of clinical trials [18, 21] provides adequate support for the concept. Indeed confidence in the safety and efficacy of tamoxifen has encouraged the clinical evaluation of tamoxifen to prevent primary disease [22]. 5 years of tamoxifen is considered to be appropriate although it is not certain whether disease will be prevented or delayed. An examination of the incidence of second primary rates in the current clinical trials might provide valuable information to use in planning the best prevention strategy. In fact the biology of the breast cancer might be very different in the primary and the metastatic lesion. Tamoxifen might prevent the development of the majority of primary disease that is genetically stable and cannot adapt to the action of tamoxifen. However, the clonal variation and genetic instability of metastatic disease might ultimately predestine the failure of long-term tamoxifen therapy. Recurrences could be hormone-independent or dependent upon the oestrogen-like properties of tamoxifen. Although a precise clinical description of the phenomenon has not been reported, tamoxifen-stimulated metastatic breast cancer growth has been described in the laboratory [23]. Pure anti-oestrogens [24] that control tumour growth [25] will soon be tested in the clinic and it is hoped that they might provide an advantage for the patient following disease recurrence during tamoxifen therapy.

To return to the central theme of "are we giving tamoxifen for too long?", it is fair to say that we have not yet evaluated the benefits that might accrue from prolonged tamoxifen therapy. Clearly a minority of patients, though we do not know who, will benefit from the antitumour properties of tamoxifen and hopefully the survival advantage observed in adjuvant trials will be maintained during long-term therapy. Indeed, if tamoxifen can provide additional benefits with regard to non-cancer-related deaths then tamoxifen therapy will clearly become the maintenance therapy of choice in all women following a diagnosis of breast cancer.

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Clinician Surrogates and Equipoise: an Analogy to Lawyers who Represent Themselves?

DESPITE THE apparent increase in our knowledge of the biology of cancer, the process of decision-making in cancer management has become much more complex, and, in many ways, a much less certain procedure. With the increasing sophistication of the design of clinical trials and the proliferation of the available treatment options, the choices facing clinicians and their patients have become increasingly complicated.

Recently, a greater level of attention has been directed to the study of the decision-making process among patients and clinicians, including the introduction of the clinician surrogate model [1]. This model involves the assessment of responses by disinterested medical experts to detailed questionnaires on controversial issues of medical management. It has been postulated that such experts may provide more useful information than is available from patient surveys regarding choice of available treatment and the ethics of clinical trials [2, 3]. With the burgeoning number of reports of such studies [2, 4–6], it appears that increasing resources are likely to be expended in the application of the model, and it is time to assess whether this work is likely to advance our knowledge.

The decision to treat a particular neoplasm in a certain way is predicated on a broad range of factors: those that pertain to the community, the tumour, the patient and the doctor. Community issues include the available resources and funding, attitudes to cancer, and the pattern and extent of competing health problems. Tumour-related factors include the biology of the disease *per se*, the range of available treatments and the likely outcomes of such treatment. Indices relevant to the treatment of an individual patient include age, sex, physical state, mental and cognitive function, education, the extent and nature of prior treatment, compliance in the treatment regimen, the patient's understanding of the disease and its prognosis, and issues pertaining to "informed" and "cognisant" consent (one should perhaps draw a distinction between the provision of information and the real comprehension and application of such information by the patient).

Based upon remarkably scant objective data, an increasingly stringent medicolegal approach has evolved with respect to the factors governing the choice of treatment, and in particular to the quality of informed consent. However, many of us have come to believe that informed consent may really be a medical oxymoron, and that most patients simply do not have the background or training to give fully informed and cognisant consent regarding all of the relevant issues [5, 7]. The patient's understanding of these issues will be predicated on the nature and format of information provided and on the methods of information transfer [8–11]. We have previously shown in a randomised trial of consent procedures that the combination of verbal discussion and a written information sheet produces a greater level of comprehension and retained information than verbal communication alone [12], an observation confirmed by others [11]. Of importance, this increased level of understanding was achieved at the expense of a significantly greater level of patient anxiety [12].

Therefore, against this background of the patient's anxiety,

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