are known to proliferate more rapidly than in most normal tissues [17], making these cells inescapably targets for cell cycle-specific toxins. No agent is currently available which specifically recognises endothelial cells within tumours. Indeed, while the endothelial cell is increasingly recognised as a potential target for therapy, the likely consequences for the tumour of direct damage to its associated endothelial cells are still unknown and a matter of speculation. A toxin derived from group B staphylococcus has recenty been described which preferentially binds to "immature" endothelium (a characteristic frequently attributed to endothelial cells associated with tumours), and produces haemorrhagic necrosis in human tumour xenografts [18]. Further investigations with this agent should provide some interesting data.

The potential therapeutic benefit of damage to the vasculature and, more specifically, the endothelial cells of tumours by conventional chemotherapeutic agents seems, for the most part, to have been overlooked. Nevertheless, the perceived boundary separating those agents which kill tumour cells directly, and those, like FAA (and now vinblastine), which exploit subtle but powerful biological mechanisms involving a complex interplay of vascular damage and immune effector cells, is becoming blurred. Perhaps we should pause and re-examine the mechanisms of action of other "conventional" chemotherapeutic agents. By the very nature of the way in which chemotherapeutic agents are screened, we may be overlooking some interesting new candidates. A better understanding of the role of the vasculature in tumour response to systemic therapy might just be an added bonus.

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# Dilemmas in the Development of Cytoxic Drug Analogues

THE PAPER by Herait and colleagues on the early clinical assessment of a new anthracycline analogue (pirarubicin) in this month's *European Journal of Cancer* (**28**, 1670–1676), highlights the issue of using historical data to establish the relative cost-benefit of new compounds. The authors argue that the randomised clinical trial is an inappropriate way of determining whether a new drug is less toxic at an equi-effective dose than a standard drug, largely because of the difficulty of recruiting adequate numbers of patients into phase III studies. They suggest that 'historical comparisons, though they are unable to replace randomised studies, may be relevant for an *early* evaluation of the drug and can lead to further decisions on the development of phase III studies'.

Revised and accepted 1 Apr. 1992

Herait and colleagues are to be commended for making explicit an important concern about the best use of patient resources for new analogue development. Analogues are an important aspect of new drug development while—paradoxically, given that cancer is the second cause of mortality in the western world—patient resources for clinical trials are quite limited. Because of this it makes sense to curtail the need for large and expensive clinical trials by identifying new and more appropriate ways of comparing analogues with parent compounds.

The crucial issue, however, is not the methodology of comparison—where the randomised clinical trial is the recognised 'gold' [1] standard—but rather the subject of comparison (i.e. the choice of analogue). If so, the potential waste of patient resources needs to be addressed at a much earlier stage in the development of new analogues (or drugs for that matter). At this preclinical decision-point a new compound would either be rejected or accepted for clinical investigation.

There are three main reasons for seeking new analogues: non-cross-resistant activity, less toxicity, or ease of drug administration (ideally all three). Looking for a wider spectrum of activity, or lack of cross-resistance, is a relatively easy matter in terms of clinical trial methodology. For example a 20% complete remission (CR) rate in a phase II trial in advanced untreated colon or lung patients would provide convincing evidence that a new agent should be taken seriously without the need to embark on early large scale trials. These of course would need to be carried out eventually and also need to be large assuming a requirement to detect moderate survival differences. The difficulty is not in the way the compound is 'clinically developed' but rather in the choice of the compound itself. Clearly it is not an easy task to pick a potential winner from a preclinical screen. Many screening models have been used and abandoned and new approaches are currently being subjected to stringent scrutiny. The issue is one of preclinical rather than clinical research methodology.

When amelioration of toxicity is the prime reason for developing an analogue, activity must remain a secondary but pivotal end-point. This is particularly true if the intention is to develop an analogue of a drug which is used with a curative intent (leukaemias, testicular cancer, etc.) where it would be unacceptable (for doctors and patients) to accept a reduction in efficacy even if there was a concomitant decrease in toxicity. Hence expensive, large, null hypothesis, efficacy testing trials are the logical consequence of the development of new, possibly less toxic analogues. A prospective meta-analysis of several smaller trials is (perhaps) a practical alternative, but certainly not a conceptual one (nor less resource-consuming) as Herait *et al.* seem to suggest. The investigator should be fairly well convinced of the lower toxicity of a 'less toxic analogue' before entering it into a phase I study.

What have we learned from the long saga of anthracycline derivatives? As correctly pointed out in the *European Journal of Cancer* [2], there is a need to improve our strategy for the clinical development of analogues, and, importantly, to interpret and exploit the wealth of available data on structure–activity relationships and toxicology in order to select the most promising candidates for clinical development.

It is clear that this is more easily said than done. However the problems facing those responsible for preclinical drug development should not be transposed to the clinical setting. An excessive number of analogues each with a slender chance of success are being brought to the clinic. They quickly enter phase I investigation because of the demand for new compounds, pass through phase II and end up bottle-necked in phase III. Once there, they cannot be rescued by compromising the standards of clinical research.

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# Breast Awareness: What Do We Really Mean?

BRITISH WOMEN were thrown into a state of confusion and dismay by a controversy over breast self-examination, which was sparked by a comment from the previous Chief Medical Officer for England who suggested that it is a waste of time for women to subject themselves to the monthly ritual of feeling and looking for breast lumps when a mammogram does the same job more effectively.

Predictably, there was an immediate media response. Exhibiting variable degrees of expertise, journalists of all sorts pounced on this juicy bone: opinions were prolific and bewildered women jammed the helplines. Guidelines were issued subsequently on what we are now instructed to call "breast awareness".

I have no quarrel with that description. It is a term I have used with conviction for some 3 years, ever since a meeting convened by the late Dr Maureen Roberts (Director of the Edinburgh Screening Unit), where it was agreed by those present, including Sir Patrick Forrest and Professor Jocelyn Chamberlain, that while it was important that every effort should be made to encourage eligible women—those aged between aged 50 and 64—to enter the recently launched national breast screening programme, younger and older women should not be forgotten.

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