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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The consensus on that occasion, which has since been widely accepted, was that the concept of breast awareness should be promoted. This means looking for change in a regular but non-ritualistic way so that a woman may become familiar with her breasts and feel comfortable about handling them. She needs to learn how to distinguish between normal fluctuations and abnormal change, the latter always to be reported to her doctor.

Such advice in no way conflicts with the now widely disseminated lay perception that mammography plays the major role in detecting early breast cancers. The better than expected uptake of the screening programme (71%, as against Forrest's recommendation that 70% is the minimum essential for success) has been rewarded with a cancer detection rate of 6.2 per 1000 in the first full year of running (1st April 1990 to 31st March 1991), which compares with the 5.5 per 1000 predicted by Forrest [1]. These results show that, not only has the message been received, but it is also being acted upon.

Of course, there is no room for complacency. It is vitally important to consolidate this promising beginning and make sure that, not only those women already enrolled in the programme return for their subsequent screens, but also that their younger sisters enter as their turn comes. This they will only do if they can be persuaded to see the benefits of screening. It is, after all, not an especially enticing proposition to consent to a medical examination involving an uncomfortable procedure which might just produce a most unwelcome result.

Although improved detection should lead to improved mortality figures, and this is clearly of the utmost importance for the NHS, especially when considering cost-effectiveness, the programme has no long-term chance of success unless the benefit is also acceptable from a more individualistic perspective. Each eligible woman must feel confident that it is worth her while to enter this programme because there is a value for her in early detection; furthermore, that mammography offers her the best opportunity of achieving it. The question she therefore has to ask is: will a mammogram improve my chance of living longer with a decent quality of life if a cancer is detected?

This is a tough question, as I know from the numbers of women who have informally sought my advice, and it is one that many doctors would perhaps prefer to duck, quite understandably, since a cure is a promise they cannot make. What is wrong with the truth, which, to quote Dr Helen Stewart of the Scottish Cancer Trials Office, is that "...early diagnosis makes treatment easier, even if we cannot say that it increases cure rates" [2].

The big questions about mortality and cure rates have no hope of ever being answered if women fail to enter in sufficient numbers into the programme. What could hold them back? I suggest three factors: (1) adverse publicity of the kind we saw recently when the *Sunday Times* misleadingly reported a Canadian trial (results not yet published) which suggested that mammograms caused cancer in women under 50 [3]; (2) unresolved disputes between the professionals about the pros and cons of screening which journalists report with glee but little balance; and (3) doctors who discourage women from doing breast self-examination.

The third point is probably the most significant because if women are not encouraged to take sensible precautionary health measures when they are younger and probably more responsive, they are less likely to come forward later in life for what may seem then to be no more than another medical fad. Although not wholly comparable, a lesson can be drawn from the cervical screening programme where two-thirds of the women who die from cervical cancer have never been screened and most of the late-stage cancers are diagnosed in older women.

Breast cancer is the main cause of death in British women aged between 35 and 54 and this age band accounts for more than one-fifth of the annual incidence [4]. It would be wrong if women in these unscreened age groups as well as those who are past the screening age were made to feel inhibited about breast self-examination. Even though the cancer they may discover is likely to be clinically later than most cancers detected by mammography, the same truth applies: a prompt diagnosis offers a more acceptable treatment and an improved quality of survival. Let us not forget that more than 90% of breast lumps are discovered by the women who have them. If they do not report them, who will?

Technology, though important, does not and never should reign surpreme in health care. 10 years from now, the mammogram may have been ousted by a better, less intrusive method of detection. Even so, there will always remain a case for informing a healthy, if at-risk population, about sensible preventative measures they can take on their behalf. Too much medicalisation imposed by enthusiastic professionals tends to sap the common will to take responsibility for our own health.

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