Cancer chemotherapy celebrated its fiftieth anniversary last year. It was in 1945 that wartime research on the nitrogen mustards, which uncovered their potential use in the treatment of leukaemias and other cancers, was first made public. Fifty years later, more than sixty drugs have been registered in the USA for the treatment of cancer, but there are still lessons to be learnt.

One problem, paradoxically, is that many anticancer agents produce a response in several different classes of the disease. This means that once a new agent has been shown to be effective in one cancer, much effort is devoted to further investigations of the same drug in various combinations for different disorders. While this approach has led to advances in the treatment of many childhood cancers and some rare diseases, a plethora of studies on metastatic colon cancer, for example, has yielded little benefit. 5-fluorouracil continues to be used in trials, yet there is no evidence for an increase in survival. The lesson to be learnt is that many common cancers are not adequately treated by present-day chemotherapy, and most trials of this sort are a waste of time. Significant increases in survival will only occur if the selectivity of present-day anticancer agents can be increased or new classes of more selective agents can be discovered. There are two fundamental problems in drug development: a lack of suitable laboratory tests and the difficulty of conducting early clinical trials. Firstly, no existing laboratory method can accurately predict which chemical will be effective against a particular class of human cancer. At best, tests can demonstrate a general ‘anticancer’ property. This is well exemplified by the discovery of cisplatin. The fact that cisplatin caused regression in a number of transplanted rodent tumours created no great excitement amongst chemotherapists. It was only later when it was tested clinically against ovarian cancer that results were sufficiently positive to encourage others to investigate. Only then was it discovered that metastatic teratoma was extraordinarily sensitive to the drug. This finding was made as a result of phase II trials and no laboratory model could have predicted it. The lesson to be learnt is that new drugs should be tested extensively in phase II trials before they are discarded.

The second problem concerns early clinical trials. Because new drugs can only be tested against advanced and usually heavily pretreated disease, it is unlikely that dramatic responses will occur. The methods used to detect responses in solid tumours and metastases are crude, and it is likely that many useful drugs are missed. New techniques are needed to detect small but important responses.

In addition to these technical problems, clinical trials are expensive and the time required for preclinical pharmacology and toxicology is lengthy. In the early days, drugs could enter clinical trials after fairly simple toxicological studies. The thalidomide disaster in the 1960s, however, led to the setting up of regulatory bodies to scrutinize drugs before clinical trials. This proved detrimental for cancer drug development because a series of fairly long-term tests is now required. These must be carried out in both rodents and one other species, usually the dog. This approach was probably a good thing for most medicines where a large margin of safety is required between the therapeutic dose and the dose which causes side effects, but was inappropriate for anticancer agents which are tested at the maximum possible dose which gives manageable side effects. These new regulations meant that the cost of one clinical trial after the 1970s was equivalent to the cost of ten before that time.

Solutions to these problems are available, although to put them into practice would require the cooperation of government regulatory authorities, the pharmaceutical industry and other organisations such as the US National Cancer Institute (NCI), the UK Cancer Research Campaign (CRC) and the European Organisation for Research and Treatment of Cancer (EORTC). Firstly, it is important to switch from clinical trials of analogues and combinations of standard drugs to trials of new classes of anticancer agents. Further, an international effort should be launched whereby...
these new agents can be rapidly tested in phase II trials against common solid cancers using new techniques to detect small but significant tumour responses. Lead chemicals discovered in this way could then be taken back to the laboratory for further development. There is no shortage of new drugs which act by mechanisms quite different from present-day agents, and new approaches can greatly increase the amount of cytotoxic agents delivered to solid tumours.

As long ago as 1980, the CRC introduced protocols which enabled early clinical trials to be carried out rapidly and with minimal cost. These procedures used short-term tests only in rodents to determine a safe starting dose. The test can be completed within six months and around fifty clinical trials using this protocol have been successfully carried out in collaboration with the EORTC. Despite this, the American Food and Drug Administration (FDA), regulatory authorities in many other countries and many drug companies still insist on using a second animal species before a phase I clinical trial is permitted instead of using the money spent to develop several agents with minimal toxicology testing. The EORTC and CRC also plan to introduce positron emission tomographic scanning into early clinical trials as a highly sensitive method of measuring tumour response.

Cancer mortality has changed little over the past forty years, mainly because of our failure to develop curative chemotherapy for the common solid cancers. The way forward is to carry out extensive phase I and II clinical trials of the many new types of anticancer agent that have become available as a result of increased knowledge about cancer cells and how they differ from normal tissues. In order to do this, the regulatory authorities must recognize that minimal toxicology protocols are adequate, and drug companies must be persuaded to give more emphasis to the search for new chemotherapeutic agents. A coordinated effort to achieve these aims would be a wonderful way to mark the fiftieth anniversary of modern chemotherapy. Unfortunately the regulatory authorities find it less risky to stick with extensive safety testing rather than to use shortcuts, however well-validated clinically. Many but not all drug companies, mindful of profits, prefer the easy way out and concentrate on analogues, while most clinicians opt for trials of combinations of known agents, being aware that they are worth a publication or two.