Critical Review of Problems of Chemotherapy

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During the 1930s progress was made in the identification of substances which induce cancer. This work has led to the removal of some carcinogens from the environment. The advance started with the discoveries by Kennaway (1930) and Cook (1933) of the carcinogenic polycyclic hydrocarbons and of Yoshida (1934) that the azo dye, amino-azotoluene, induced liver cancer. The two aspects of the cancer problem, the causation of the disease and its treatment by chemical compounds, were united by the discovery of Haddow (*see* 1937) that carcinogenic compounds inhibited the growth of normal and of cancer tissues. Since this discovery these two approaches to the cancer problem, the enquiry into the causes and the investigation into the treatment by chemical compounds, have been associated at any rate as far as fundamental research is concerned.

Since the Second World War the emphasis on research has changed, as far as numbers of investigators and resources are concerned, from carcinogenesis to chemotherapy. Before 1939 very few workers were interested in therapy but they included Dr M J Shear in U.S.A. and Professor A Haddow and myself in Britain. Now there are hundreds of investigators looking for new chemotherapeutic agents.

The direction as well as the volume of research into cancer chemotherapy was changed considerably by the discovery during the war that some nitrogen mustards (Formulary I, II), which were potential war gases, were effective in controlling some forms of cancer, notably Hodgkin's disease. This discovery was made independently in England in 1942 by Wilkinson & Fletcher (1947) and in the United States in 1943 by Goodman *et al.* (1946). In both cases the discoveries were made by clinicians who tried the compounds long before there was any evidence that nitrogen mustards had any effect on tumours growing in animals. The compounds were investigated because of their known leucopenic action in animals and also in men who had been accidentally exposed to vesicants of this type. The original discovery of the effect of simple chlorethylamines or nitrogen mustards in controlling lymphadenomas was thus a product of war research, and it is possible this effect would still not be known had it not been for the war. The discovery of the mutagenic effect of mustard gas and nitrogen mustards by Auerbach & Robson (1947) was similarly a byproduct of wartime research into the biological effects of poison gas.

Since the demonstration of the beneficial effect of the original nitrogen mustard derivatives HN2 and HN3 (Formulary I, II) some hundreds of related compounds have been synthesized and tested in animals for their effect in inhibiting the growth of tumours. *Cancer Chemotherapy Reports* (1963) lists 2,200 alkylating agents which have been tested against animal tumours. This does not include the methane sulphonic esters such as Myleran (Formulary VII). A great deal of ingenuity and careful work has been expended in many countries of the world, but the results are difficult to assess. One curious result is that many countries have their own compounds which appear to be more effective in the country of origin than elsewhere (*see* Table 1). One is reminded of the remark of the late Dr J W Trevan who said during one of his lectures that it was difficult to show that a drug was of real value in treatment of a disease and impossible to show that one was better than another. In the last few years, however, clinical trials to determine which of two drugs was the more effective have been carried out on a scale which Dr Trevan could not have thought possible.

Table 1
Favourite anti-cancer drugs in different countries

Country	*Compounds used*
Japan	Nitromin
USSR	Sarcolysin, dopan
Germany	Ethylenimoquinones, cyclophosphamide
Hungary	Mannitol mustard (Degranol)
Britain	Myleran, chlorambucil, melphalan
USA	ThioTEPA, tretamine (TEM)

All the many compounds of this group which have been synthesized and tested are alkylating agents and presumably have similar fundamental chemical actions on the cell and it is not surprising that they are all somewhat similar in their effects. From a biochemical point of view it is difficult to understand why some methane sulphonic acid ester derivatives like Myleran should affect mainly myeloid cells, and chloroethylamine derivatives such as chlorambucil (Formulary V) and ethylenimine derivatives such as tretamine (TEM; Formulary IX) and thioTEPA (Formulary Xa) should have more effect on lymphocytes. The animal experiments of Elson (1963) and the clinical investigations of Galton and his colleagues (*see* Galton 1960) have shown, however, that there are real differences. Among the advantages of these newer alkylating agents are the ease of administration and the fact that they produce fewer undesirable side-effects in patients.

The early history of the use of the antifolic acid compounds in the treatment of acute leukæmia is similar to that of the nitrogen mustard

derivatives in that they were used clinically before it had been shown that they had antitumour activity in animals. Earlier work had suggested that some natural folic acid derivatives (e.g. teropterin) inhibited the growth of some tumours in mice but the folic acid (Formulary XI) analogue, aminopterin (Formulary XIa), had only been demonstrated to inhibit growth of bacteria *Lactobacillus casei* and *Streptococcus fæcalis* before Farber *et al.* (1948) showed that it produced remissions in children with acute leukæmia. Aminopterin is a very toxic substance. It is remarkable, from a chemical point of view, that the replacement of a hydroxyl group in the molecule of the vitamin folic acid (Formulary XI) by an amino group produces aminopterin which is an antagonist and a very poisonous compound. Soon after aminopterin had been introduced it was found that the 10-methyl derivative which became known as amethopterin (Formulary XIb) was less toxic, but an effective drug in the control of acute leukæmia. After the introduction of these compounds as drugs for leukæmia in children, animal leukæmias were found which could be controlled by them. The use of animal leukæmias and of other biological systems has given us some insight into the mode of action of the drugs and some indication of the way in which drug resistance develops. The use of the animal leukæmias and tumours up to the present time, however, has not led to the introduction of better drugs than amethopterin (Formulary XIb).

In the past few years amethopterin has been employed in the treatment of tumours of the breast, and of chorio-epithelioma. It has also been used in treatment of tumours of the head and neck and other sites by local perfusion. In these developments also animal experimentation has given little help to the clinicians who have made these advances.

All the known agents used in the treatment of cancer and of leukæmia suffer from the disadvantage that they become ineffective because the disease becomes resistant. It is obvious that, to avoid the development of resistance, combination therapy with two or more drugs should be used as in the treatment of tuberculosis. Development of resistance is more likely to occur with the nitrogen mustard derivatives which are mutagens, than with drugs which are not mutagenic. The treatment will increase the incidence of new types of cell, some of which may be resistant to the drug.

Therapy with two drugs given simultaneously should be used in the treatment of cancer for at least two reasons. In the first place, because the different cells in tumours probably vary in their behaviour, the use of two agents is more likely to be effective. A more important reason is that resistant cells are less likely to arise if two different agents are present. If cells arise which are resistant to one agent by mutation or an analogous change, then they should be controlled by the second agent. The development of resistance to two agents simultaneously is very unlikely to occur.

Table 2
Chemotherapy of various types of neoplastic disease

Disease	*Drugs*
Hodgkin's disease	HN2, chlorambucil, actinomycin C, vinblastine
Chronic granulocytic leukæmia	Myleran, 6-mercaptopurine, mitomycin C
Chronic lymphocytic leukæmia	chlorambucil, thioTEPA, corticosteroids
Acute leukæmia in children	6-mercaptopurine, amethopterin, corticosteroids
Polycythæmia vera	dopan, novoembichin
Multiple myeloma	melphalan, cyclophosphamide, urethane
Lymphosarcoma	chlorambucil, HN2
Ewing's sarcoma	sarcolysin, melphalan
Seminoma	melphalan
Choriocarcinoma	amethopterin
Wilms's tumour	actinomycin D
Prostate carcinoma	œstrogens
Breast carcinoma	androgens, œstrogens, corticosteroids amethopterin, 5-flourouracil
Ovarian carcinoma	thioTEPA, TEM, chlorambucil
Skin carcinoma	colchamine (ointment)

One of the reasons why combination therapy has not been employed is that so few agents were available. Many compounds, however, are now available; some of these are listed in Table 2 (*see also* Formulary I-XI). There would seem little point in trying combination therapy with two alkylating agents, for example, as these agents all act by the same mechanism. Simultaneous administration of an antimetabolite and an alkylating agent would, however, probably be better than the sequential use of two types of agent and should reduce the possibility of resistance developing. One disadvantage of combination therapy is that it is difficult to know which of the drugs used is producing any effect. It is hard to assess the improvement in condition from the use of a single drug, and if combination therapy is used the interpretation of results is even more difficult. In spite of this, however, I think that it should be used more extensively.

One particular combination which seems worth trial is that of an alkylating agent such as chlorambucil or melphalan with one of the 5-fluorouracil derivatives which are antimetabolites. The alkylating agent would destroy nucleic acid in the cells as a result of which nucleic acid synthesis should be increased. In the presence of 5-fluorouracil an increased 'lethal synthesis' of abnormal nucleic acid would occur. Other antimetabolites which are known to inhibit particular stages of nucleic acid synthesis, such as methotrexate and 6-mercaptopurine, might also be usefully used in combination with alkylating agents.

The fact that there has been so much expendi-

ture in experimental chemotherapy with apparently so little result would perhaps warrant an enquiry into the methods of experimental cancer chemotherapy. Early experience of clinical chemotherapy and in experimental chemotherapy of cancer has indicated that different tumours respond to different drugs (cf. Table 2). Some patients with tumours of the prostate and of the breast benefit from the use of œstrogens, and some with lymphosarcomas are improved by treatment with nitrogen mustards. These findings indicate that any one drug is likely to be effective against one kind of tumour. For this reason new compounds should be tested against a range or spectrum of tumours as I have advocated for some time (*see* Boyland 1948). In the United States thousands of compounds have been screened against three tumours without very much success. Recently the Americans have outlined testing procedures with a large number of tumours and the use of these should be more effective. In Russia a series of twelve different animal tumours is used. The Chinese, who started cancer research some four years ago, are also using the same twelve animal tumours in their chemotherapy research.

A difficult problem in the chemotherapy of cancer is to decide which drug to use in any particular type of cancer. Having decided that a compound is worth trying in the treatment of human cancer, either as the result of animal experiments, for theoretical or other reasons, the clinician must decide against which type of tumour the substance must be tried. It is this decision which seems to be the key to successful chemotherapy. The Russian workers tried sarcolysin (Formulary VI) against seminomas and myeloma among other forms of tumours and found that it was effective particularly against these tumours. In the last few years melphalan (Formulary VI), which is a more active form of sarcolysin, has been used effectively in the treatment of cancer by local perfusion. It is possible that other compounds would be more effective when used in this way. Because this stage of the clinical application of drugs in the treatment of cancer is so difficult, I think that this aspect of the problem needs more emphasis, and in the United States considerable facilities are now available for the clinical trial of new drugs.

The properties of a substance which is to be used for the treatment of cancer by local perfusion probably differ from those which are required if the compound is going to be given systemically; for this reason it would be advisable to have experimental procedures whereby different drugs could be tested against animal tumours by regional perfusion. With experiments on tumours in dogs it is possible to get some idea of the extent of the uptake of the drug, and of the degree of damage which is produced in the normal tissues (Boyland *et al.* 1961). Such experiments can only be carried out at present with tumours in large animals such as dogs and these are difficult to produce, but if there is any future in the use of local perfusion then experiments of this type to determine the best drug for use in this way should be carried out.

Another way in which it is hoped to find out which particular tumour in man is likely to be susceptible to a particular drug is the use of tissue culture. Many human tumours can be grown in tissue culture, and the effect of local application of a range of chemical compounds can be tested in the laboratory. If trials of this kind show that tumours which are susceptible when grown in tissue culture are also sensitive to the same drug given to man, then this method of choosing drugs should be of great value. I think, however, that the blood supply to tumours is most important in any form of therapy. In tissue culture, this factor is not present. One way of increasing the effectiveness of chemotherapy of cancer would be to introduce some drug which would locally and possibly temporarily increase the blood supply to particular tumours, so that the drug was carried to the tumour. The possibility of Ronicol (3-pyridinemethanol) doing so merits investigation.

There are many fresh techniques which should be applied to the problem of the chemotherapy of cancer. I think that a large proportion of cancer is produced by external factors which could be avoided and this is one way of tackling the cancer problem, but even if we knew what the external factors were it would take a long time to remove them to prevent cancer in this way. Also, as I have said, the basic biochemical problems of carcinogenesis and chemotherapy are to some extent interrelated so that progress in the two aspects of the problem is likely to go hand in hand and there is need for more work on both sides of the problem. If experimental carcinogenesis and chemotherapy of cancer are opposed, it is only as finger and thumb are opposed and the threat of cancer will be squeezed out between the two.

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