# THE TREATMENT OF CANCER

## WITH SPECIAL REFERENCE TO RADIOTHERAPY AND CHEMOTHERAPY

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# PREFACE

This book is a record of one of the courses organized by the School of Clinical Research and Postgraduate Medical Teaching of the University of Cambridge. We are attempting in these courses to consider recent developments in various aspects of medicine with particular reference to their scientific basis. It is essential for us to take part in and utilize to the full the advances in the scientific understanding of medicine. Nevertheless, the well-founded practical approach, combined with human kindness, is needed as much as ever in clinical medicine.

Similar courses have already been held on 'Progress in the biological sciences in relation to dermatology', 'Depression as a problem in psychiatry', and 'Haematology'.

In this book, we are interested in attempts to improve the treatment of patients with cancer. Emphasis is laid on the scientific basis of some of the more recent developments in our knowledge of cancer. It is now generally accepted that progress in this branch of medical science requires the collaboration of workers in a wide range of disciplines. The serious practical problems of the care of patients with cancer are not neglected, as shown, for example, by the contributions on the problem of advanced malignancy and the treatment of pain.

The discussions were an important feature of the course. In the discussions an attempt was made to bring out useful aspects of the contributions of medical science to clinical practice and to think about the possibilities of new methods of treatment. The reports of the discussions have been edited and considerably abridged. All but one of the papers given during the course are included in this book.

I wish to take this opportunity of thanking the lecturers for their help and tolerance and the participants in the course for their valuable cooperation and contributions to the discussion. It is a pleasure too to acknowledge my indebtedness to my secretary Miss M. J. Crichton for her help, especially with the transcription of the tape recordings, to Mr J. W. Woodcock, Secretary of the Medical School and to Dr D. B. Cater and Dr S. D. Sturton for assistance in preparing the manuscript for the press.

This book has been prepared in the hope that it may be a contribution to medical learning. I wish to express my thanks to the Syndics of the Cambridge University Press for continued support in the publication of the new series of Cambridge medical books.

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# CONTENTS

# NEWER DEVELOPMENTS IN CARCINO-CHEMOTHERAPY

By F. BERGEL

It was suggested that I should give a brief review of the role of chemicals (in the widest sense of the word) in the treatment of neoplastic diseases. It is today a commonplace statement that, apart from the systemic use of a number of drugs effecting mainly palliation and in a few cases cures, at present the principal interest and hope of everybody active in this field centres on combinations of surgery and radiotherapy, or both, with chemotherapy. The favourable outcome of this depends largely on an increased knowledge of the biochemical behaviour of human cancers. I shall give you first a few examples which should illustrate this general theme, and also remind you of the more important cytotoxic agents currently applied by clinicians.

In the forefront are the biological alkylating agents and antimetabolites with the nitrogen mustards, the methanesulphonates and the ethyleneimines among the former, and antipyrimidines, antipurines and antifolics, among the latter. More and more facts have accumulated over the last two years which may throw light on the action mechanism of the nitrogen mustards and of 'Myleran'. It is not unlikely that the mustards achieve their cytotoxic effects by interaction with the $N^7$ of the guanine unit of DNA, leading to quaternization of this nitrogen and then to a breakdown of the nucleic-acid chain. Lawley & Brookes (1960) proposed that in the case of bifunctional mustards the agent interacted with guanine units belonging to different strands of the double helix (Fig. 1). As 'Myleran', a representative of the dimethanesulphonate series, reacts much more sluggishly with DNA than the mustards, it is probable, according to Roberts & Warwick (1960), that its main action under *in vivo* conditions is with thiol-groups, of essential proteins or peptides, achieving in the process a de-thiolation (Fig. 2) with the formation and excretion of a hydroxy-tetrahydrothiophene sulphone. Reasonable hope can be expressed that these findings may be useful in the search for improved drugs.

However, before discussing these experimental and speculative aspects (in two parts), I should like to touch on various claims for clinical advances reported during the last two years or so, when it was demonstrated that limited specificity of action can already be observed with some of the older remedies. But these examples do not represent anything approaching

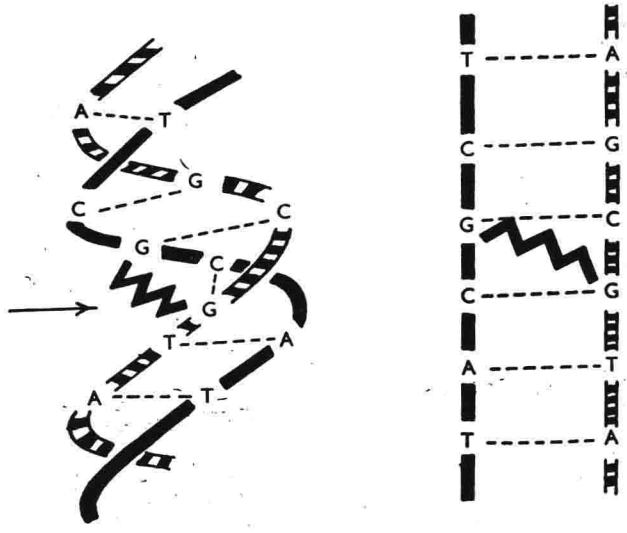



Fig. 1. Interaction of bifunctional alkylating agents. (By courtesy of Drs Lawley and Brookes.)

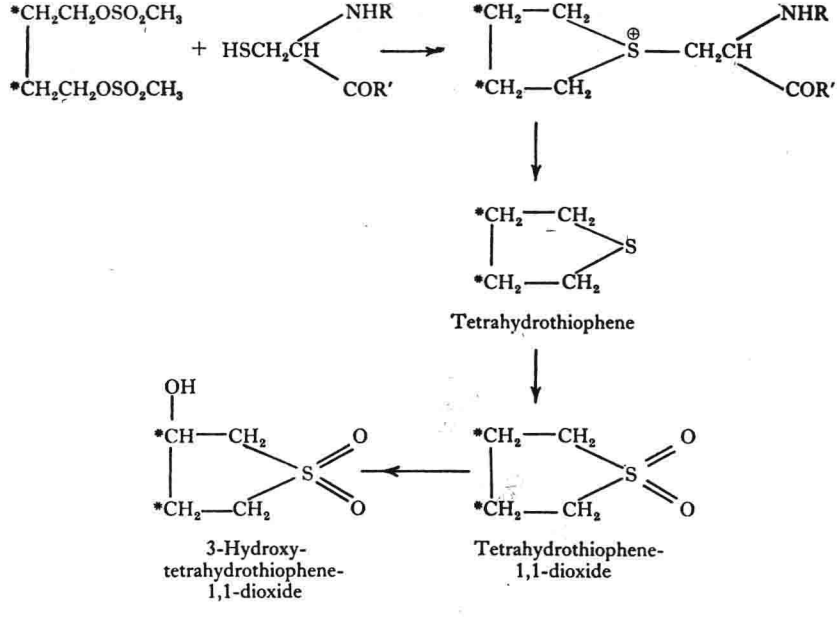
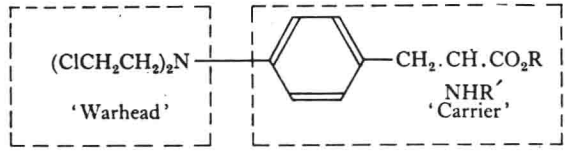



Fig. 2. The metabolic conversion of Myleran *in vivo*. (By courtesy of Drs Roberts and Warwick.)

completeness: so if I miss one or the other report on essential progress in this field, please blame the time restriction imposed on all of us.

Quite a number of drugs (HN2, thiotepa, etc.) have been used during the surgical procedure called regional perfusion (discussed at a conference* in October 1960 in New Orleans and by Mr L. A. Abel in the *B.M.J.*). But it appears that with malignant melanoma, in contrast to sarcomas and carcinomas, the mustard derivative of phenylalanine (melphalan or its racemic form merphalan, sarcolysin according to Russian workers; Fig. 3)




R = R′ = H, L — melphalan, CB 3025

R = R′ = H, D — medphalan, CB 3026

R = R′ = H, DL — merphalan, CB 3007 or sarcolysin (also o- and m-derivatives)

R = $C_2H_5$

R′ = *N*-acetylphenylalanyl, CB 3224
or leucyl CB 3262

Fig. 3. Phenylalanine derivatives (from Bergel, *Brit. Med. J.*, 1961, ii, 399).

showed some advantages over other drugs, perhaps due to its half-life as effective compound in the perfusion fluid and its possibly selective action on melanoma cells. The latter was demonstrated by E. J. Ambrose *et al.* with a suspension culture from a human biopsy sample, showing considerable susceptibility to the cytotoxic effect of the drug. The present state of treatment of malignant melanoma was recently reviewed by Sir Stanford Cade during his delivery of the Bradshaw Lecture at the Royal College of Surgeons of England. But the treatment of a Mrs L. which Plate 1 illustrates (Plate 1 (a) prior to regional perfusion, Plate 1(b) over a year† after perfusion with melphalan) was carried out by Mr C. Cooling and colleagues at the Royal Marsden Hospital. It appears, and this is confirmed by Creech *et al.* (1959) and other reports, that in certain cases the combination of surgery and chemotherapy leads to considerable success, or, as with perfusion of pelvis and other more complicated anatomical sites, at least to cessation of intractable pain, and palliation. In such circumstances, where

*See *References*, Perfusion Conference.

†At time of proof reading, April 1964, the patient has no recurrence of the melanomas.

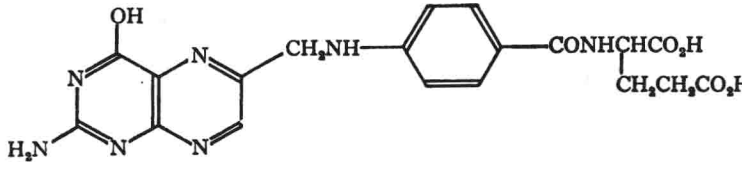
a considerable leakage of the drugs into the general circulation may take place, application of substances which efficiently counteract or destroy alkylating agents would be desirable. Studies towards the synthesis and testing of such compounds are being pursued, comprising so far a number of thiols.

Having mentioned melphalan with reference to surgical procedures it is of interest to touch upon its recent systemic use in the treatment of multiple myelomatosis, a malignant disease involving plasma cells of a number of bones, often accompanied by the production of abnormal albumin (Bence-Jones). Whether the favourable effects of the phenylalanine mustard particularly on the disease which is accompanied by the $\beta$-2A type globulin in the serum, as compared with other cytotoxic drugs, is a specific one, has to be seen.

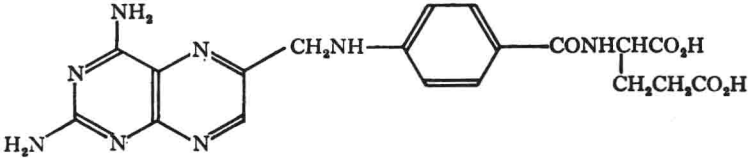
A similar problem for the biologist and biochemist arises from W. Rundle's observation that the drug cyclophosphamide, which (like our serine derivative mercasin) belongs to the group of so-called latent mustard derivatives, showed somewhat greater effectiveness on tumours of epithelial origin than other alkylating agents (20-25% of the patients). He ascribed this to its very strong and undesirable action on hair follicles and fingernails, leading to depilation and atrophy. It is of interest that the ortho-analogue of merphalan more frequently causes similar side effects than melphalan.

Apart from the use of another phosphoric acid derivative, thiotepa, for post-operative treatment of breast carcinomas with a claim for a decreased recurrence rate, I should like to mention recent successes with two drugs, not belonging to the family of alkylating agents: namely, 'Methotrexate', an antimetabolite, and actinomycin D, an antibiotic. You remember the formula of amethopterin or 'Methotrexate' as an amino-methyl analogue of folic acid (Fig. 4). It acts by interfering with the transformation of this vitamin into the enzymic cofactor formyl tetrahydrofolic acid. On 18 September a meeting took place at the Royal Society of Medicine when the application of 'Methotrexate' in the treatment of various cancers, particularly of chorionepithelioma (a tumour of the foetal membrane in pregnant women) was discussed. According to the original findings by Hertz this neoplastic disease could be practically suppressed in a good proportion of the cases for a number of years. Jumping back to combination techniques, the same drug, instead of HN2, has been used with intra-arterial injection procedures against cancers of the head and neck and other inoperable tumours.

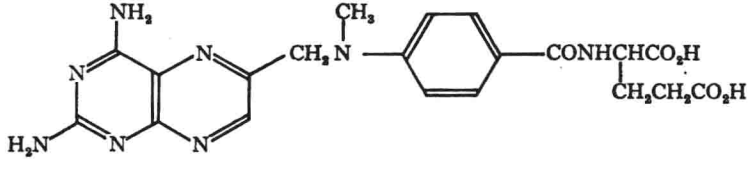
Now follow a few remarks on the application of combined radio- and chemotherapy. The classical example of a quasi-synergistic effect is that




Folic acid (PGA)




Aminopterin




Amethopterin
(Methotrexate)

Fig. 4. Folic acid and antagonists (from Bergel, *Brit. Med. J.*, 1961, ii, 399).

described by Mitchell *et al.* (Mitchell, 1948) with 'Synkavit' and X-rays. To discuss this in any detail would be truly a case of carrying coals to Newcastle. The example I should like to mention is that of actinomycin D (Fig. 5) because I had the privilege, while in Boston, of seeing there some of the clinical effects against Wilm's tumour in children as achieved by Farber, D'Angio and others. The whole matter was presented in detail during a special session of the New York Academy of Science in 1960, when the authors disclosed the experimental and clinical background. As empiricists we are delighted by any success, however limited. As theoretists we wish to know more about the reason why this kind of molecule potentiates the effects of X-rays. While the irradiation angle is a research subject for the radiophysicist and biologist, the chemists could study the molecular conditions of the antibiotic which are essential for the specific properties. Maybe the work by Gale *et al.* on the combination of actinomycin with DNA could assist in the elucidation of the phenomenon.

This brings us to some of the work aiming at an improvement inside the confines of the main groups of the present-day drugs. What should we and what can we achieve?

We should obviously aim at diminished general toxicity and, in case of solid tumours, low haemotoxicity; at greater selectivity of drugs and increased susceptibility of the neoplastic tissue. You remember perhaps that H. Druckrey during a discussion in Cambridge in 1958 drew on the blackboard a pseudomathematical distribution curve which demonstrated impressively that if one could shift toxicities or susceptibilities in the right

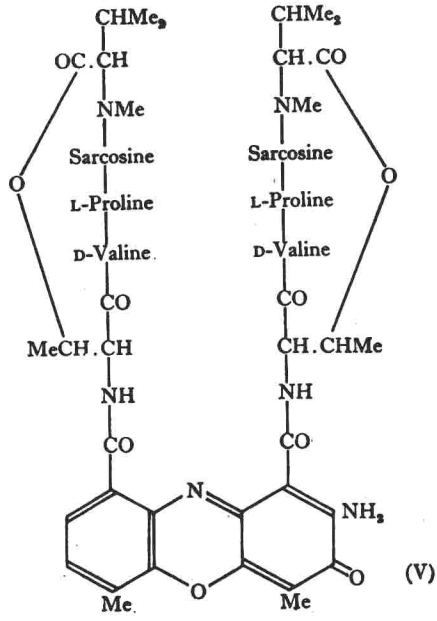



Fig. 5 Formula of actinomycin D.

direction (Fig. 6) the number of responding cancerous states or the number of useful drugs would increase satisfactorily. How can this be done practically (Table 1)? From a surgical point of view perfusion and infusion techniques could be improved. Further increase of the collaboration between radiologist and chemist, as done in Cambridge, might produce desirable developments in their combined fields. Speaking from a chemical and

Table 1. *Possible attempts at improvement of chemotherapeutic drugs*

Chemical and Physico-chemical

| Carrier Principle e.g. Peptides etc., Oligopolymers Carbohydrates etc., Lipids | 'Latent' Activity (Local release of Active Agent) | Utilization of pH-Gradients | Selective Protection of Normal Tissues | Selective Sensitization of Neoplastic Tissue |
|---|---|---|---|---|