Cancer and Chemicals

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1 Introduction

Cancer is a formidable disease that is killing increasing numbers of people every year in virtually all the countries of the world.[1] Surgery and/or radiation therapy have a great curative potential for localized tumours. Unfortunately, by the time such tumours are detected they have usually spread to other organs and the only treatment for disseminated cancer is chemotherapy, although immunotherapy holds encouraging promise for the future. The circumstances will be improved as we recognize and eliminate many of the environmental carcinogens. Some epidemiologists estimate that up to 90 per cent of all cancers are produced by environmental factors (see ref. 36).

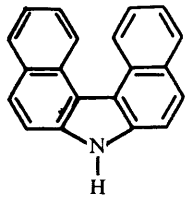
It is now generally agreed that drugs are the key factor responsible for normal life expectancy in 10 types of previously fatal cancer. This paper reviews the chemical aspects of some of the developments in cancer chemotherapy with the hope that it will attract additional chemists into the war on cancer. A brief look first at chemical carcinogenesis is appropriate.

2 Chemical Carcinogenesis

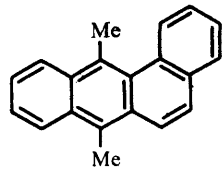
The successive steps by which a normal cell becomes malignant have not been delineated. Nevertheless, it is well known that a wide variety of chemicals can induce cancer. For the present discussion, chemical carcinogens can be divided into five groups: polycyclic aromatics, biological alkylating agents, aromatic amines and azo-compounds, *N*-nitroso-amines and -amides, and metallic substances. Examples of each group are shown in Figures 1—5.

It was recognized early that certain occupations, such as chimney sweeping, carried a high cancer risk. Recently, however, the incidence of cancer has been found to be high in a number of other types of employment, *e.g.* among nickel ore miners and workers in plants manufacturing or using vinyl chloride, bis-chloromethyl ether, asbestos, and aromatic amines. In fact, there is a higher percentage of cancer among chemists than in the general population. More and more compounds are being identified as having carcinogenic activity in animals and are therefore suspect in humans. These include relatively common compounds such as dioxan, methyl iodide, and most chlorinated hydrocarbons; this is the basis for the questions raised in the United States by the Environmental Protection Agency about the cancer risk of city water supplies which

[1] National Cancer Institute 1973 Fact Book, U.S. Department of Health, Education, and Welfare, Washington, D.C.; '75 Cancer Facts and Figures', American Cancer Society, New York, 1975.

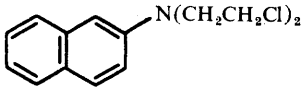


Dibenz[*c*,*g*]carbazole

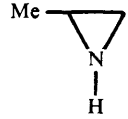


7,12-Dimethylbenz[*a*]anthracene

Figure 1 *Some polycyclic aromatic carcinogens*



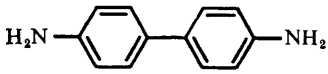
Chlornaphazin



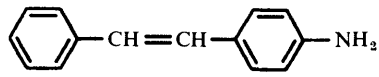
Propyleneimine

β-Propiolactone

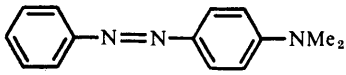
Figure 2 *Some carcinogenic alkylating agents*



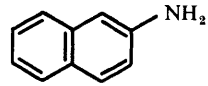
Benzidine



4-Aminostilbene



4-Dimethylaminoazobenzene



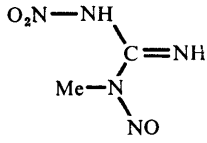
β-Naphthylamine

Figure 3 *Somecarcinogenic amines and azo-compounds*

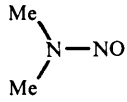
are purified by chlorination. Most chemical carcinogens are really carcinogen precursors and are activated *in vivo* by oxidizing enzymes, the so-called microsomal mixed-function oxygenases.

The work of the Pullmans on the electronic structure of carcinogenic hydrocarbons was a pioneering application of molecular orbital theory to a major biological problem.[2] They proposed that carcinogenic activity depends on the presence of a K region with high olefinic character and an L region of low reactivity {as in benz[*a*]anthracene (1) below}. More recent MO calculations have

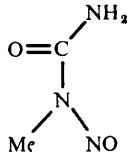
[2] A. Pullman and B. Pullman, *Adv. Cancer Res.*, 1971, **3**, 129.



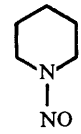
N-Methyl-*N*-nitrosonitroguanidine



N-Nitrosodimethylamine

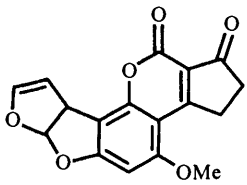


N-Methyl-*N*-nitrosourea

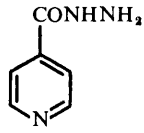


N-Nitrosopiperidine

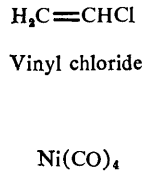
Figure 4 *Some carcinogenic* N-*nitroso-compounds*



Aflatoxin B_1



Isoniazid

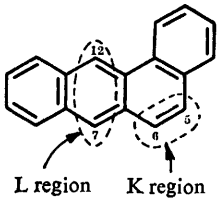


Vinyl chloride

Nickel carbonyl

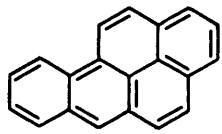
Figure 5 *Miscellaneous carcinogens*

supported this view.[3] It is interesting, for instance, that benz[*a*]pyrene (2) is carcinogenic whereas benz[*e*]pyrene (3) is not.



L region K region

(1)



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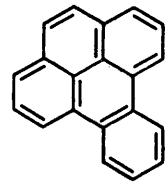


(3)

[3] L. B. Kier, 'Molecular Orbital Theory in Drug Research', Academic Press, New York 1971, p. 129; W. C. Herndon, *Trans. New York Acad. Sci.*, 1974, **36**, 200.

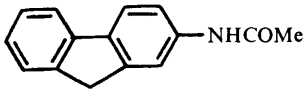
It has been proposed that the carcinogenic process involves enzymatic epoxidation of the K bond and subsequent reaction with an essential protein or nucleic acid.[4] Since most of the fluoro-derivatives of the rat liver carcinogen 4-dimethylaminoazobenzene are as active or more reactive than the parent compound, it has been proposed by analogy that if a fluoro-derivative of any of these carcinogenic aromatic amines or hydrocarbons is inactive, then the carbon which is fluorinated must occupy a critical position in the carcinogenesis process.[5] On this basis, it has been deduced that the C-5 position of benz[*a*]-anthracenes is the initial point of attack; *i.e.* all of the monofluoro-7-methylbenz-[*a*]anthracenes are carcinogenic except the 5-fluoro-isomer. Even the 6-fluoro-analogue is carcinogenic.[6] Structural studies of carcinogenic hydrocarbons attached to proteins show that, indeed, the union is at the K region of the hydrocarbons.[7,8] In some cases, the least stable K-region oxides are the most carcinogenic.[9]

The structure of the critical 'active' molecule is not known. Some work indicates that it is not the K-region epoxide itself which reacts with DNA *in vivo*.[10] Some results favour a carbocation[11] whereas other work supports the notion of a cation–radical intermediate in the biological activation.[12] The *in vitro* peroxide-catalysed binding of carcinogenic hydrocarbons to DNA has been demonstrated[13] and others[14] have induced the chemical linkage of these hydrocarbons to DNA by u.v. or *X*-ray radiation. The K-region oxides usually are more carcinogenic than the corresponding hydrocarbons, but there are exceptions.[15] Although there is not a good correlation between the binding of these hydrocarbons to DNA and their carcinogenic activity,[15,16] there are quantitative correlations of carcinogenicity with their hydrophobicity, K-region reactivity, and charge-transfer complex forming ability.[17] It has been suggested that the hydrocarbon enters the cell as a hydrocarbon, forms a loose molecular complex with the cellular component with which it is going to react, and is then activated through oxygenation by a hydroxylase enzyme.[8] It is noteworthy

[4] E. Boyland, *Biochem. Soc. Symp.*, 1950, **5**, 40; 'Chemical Carcinogenesis', Part A, ed., P.O.P. Ts'O and J. A. DiPaolo, Dekker Inc., New York, 1974.
[5] J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Res.*, 1957, **17**, 387.
[6] M. S. Newman and R. F. Cunica, *J. Medicin. Chem.*, 1972, **15**, 323.
[7] T. J. Siaga, J. D. Scribner, and J. M. Rice, *Cancer Res.*, 1973, **33**, 1032.
[8] M. Calvin, *Radiation Res.*, 1972, **50**(1), 105.
[9] S. H. Goh and R. G. Harvey, *J. Amer. Chem. Soc.*, 1973, **95**, 242.
[10] P. Brookes and W. M. Baird, *Proc. Amer. Assoc. Cancer Res.*, 1973, **14**, 30; E. Cavalieri and M. Calvin, *Photochem. and Photobiol.*, 1971, **14**, 641.
[11] E. Cavalieri and R. Auerbach, *Proc. Amer. Assoc. Cancer Res.*, 1973, **14**, 123.
[12] W. Caspary, B. Cohen, S. Lesko, and P. O. P. Ts'O, *Biochemistry*, 1973, **12**, 2649.
[13] L. E. Morreal, T. L. Dao, K. Eskins, C. L. King, and J. Dienstag, *Biochim. Biophys. Acta*, 1968, **169**, 224.
[14] S. A. Rapoport and P. O. P. Ts'O, *Proc. Nat. Acad. Sci. U.S.A.*, 1966, **55**, 381; M. Calvin, *Radiation Res.*, 1972, **50**(1), 105.
[15] D. M. Jerina and J. W. Daly, *Science*, 1974, **185**, 573.
[16] T. Kuroki, E. Huberman, H. Marquardt, J. K. Selkirk, C. Heidelberger, P. L. Grover, and P. Sims, *Chem.–Biol. Interactions*, 1972, **4**, 389.
[17] R. Franke, *Chem.–Biol. Interactions*, 1973, **6**, 1.

that there is a statistical correlation between the concentration of the arylhydrocarbon hydroxylases in individuals and the chances of getting lung cancer.[18]

To induce cancer the aromatic amines need to undergo *N*-hydroxylation.[19] One extensive study,[20] for example, has shown that *N*-(2-fluorenyl)acetamide (FAA) (4) is enzymatically oxidized[21] in the male rat liver by NADPH and oxygen to *N*-hydroxy-FAA. This is converted by 3′-phosphoadenoxyl-5′-phosphosulphate into FAA-*N*-sulphate, a highly reactive electrophile which attacks nucleophilic tissue constituents. It is significant that *N*-hydroxy-FAA is inactive in species lacking sulphotransferase, and that FAA-*N*-sulphate reacts with methionine or guanine residues to produce some of the same derivatives as obtained from the liver protein or DNA and RNA of rats given injections of *N*-hydroxy-FAA.[20] In connection with this work, a convenient method for assessing the electrophilic reactivity of these *N*-arylacethydroxamic acids has been developed.[22] Similarly 3-hydroxyxanthine (5) and 3-hydroxyguanine (6), following reaction with sulphotransferase, yield derivatives which induce tumours *via* cationic or free-radical species.[23]



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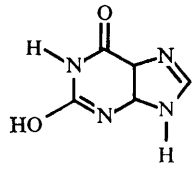

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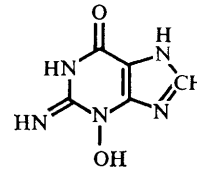

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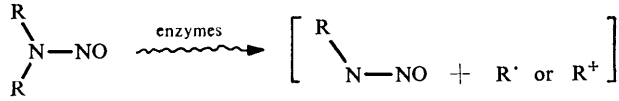
The *N*-nitroso-amines and -amides and halogen compounds are thought to be enzymatically converted into cationic or free-radical species:[24]



[18] *Cf.* T. H. Maugh, *Science*, 1974, **183**, 940.

[19] J. L. Radomski, G. M. Conzelman, jun., A. A. Rey, and E. Brill, *J. Nat. Cancer. Inst.*, 1973, **50**, 989; P. D. Lotlikar, L. Luha, and K. Zaleski, *Biochem. Biophys. Res. Comm.*, 1974, **59**, 1349.

[20] J. A. Miller and E. C. Miller, in 'Molecular Biology of Cancer', ed. H. Bush, Academic Press, New York, 1974; J. D. Scribner and N. K. Naimy, *Cancer Res.*, 1973, **33**, 1159; E. J. Barry and H. R. Gutmann, *J. Biol. Chem.*, 1973, **248**, 2730.

[21] Experiments indicate that amine oxidase is not involved in the *N*-hydroxylation: P. D. Lotikar, K. Wertman, and L. Luha, *Biochem. J.*, 1973, **136**, 1137.

[22] H. Bartsch, M. Dworkin, J. A. Miller, and E. C. Miller, *J. Medicin. Chem.*, 1974, **17**, 386.

[23] C. B. Brown, M. N. Teller, I. Smullyan, N. J. M. Birdsall, T.-C. Lee, J. C. Parham, and G. Stohrer, *Cancer Res.*, 1973, **33**, 1113.

[24] Y. Ioki, Minority Biomedical Research Seminar, California State University, Los Angeles, Nov. 14, 1974.

Skin cancers can be induced by u.v. radiation but little is known about the oncogenic sequence. U.v.-radiated proteins are carcinogenic upon subcutaneous injection whereas normal proteins are not.[25] Tyrosine and tryptophan are suspected of being the major absorbing units.[26] Either direct radiation of DNA or DNA-photoproduct interactions could produce changes in nucleic acids to induce malignancy. Biological constituents, particularly lipids, might serve as photosensitizers to trigger tumour growth, not only of skin cancer but other types as well. For instance, the carcinogen cholesterol-5α,6α-epoxide (CAE) is formed in both human and hairless mouse skin upon exposure to u.v. light.[27] The study of the mechanisms of radiation carcinogenesis offers special opportunities for photochemists to contribute to the war on cancer.

Although a definitive picture cannot be given for the role of polysaccharides in the carcinogenic process, there is some evidence that mucopolysaccharides are involved in cell–cell association and therefore affect metastasis of cancer cells. Experimental results have been reviewed recently.[28]

An experimental confluence between carcinogenesis and oxidative phosphorylation has been observed and is the basis for an hypothesis for carcinogenesis. This view proposes that a metabolite of a carcinogen interferes with the flux of energy in the mitochondria to release mitochondrial genetic material which may behave like an oncogenic virus.[29]

Certain metal salts and metallo-organics are rapid-acting carcinogens in animals, notably cadmium and nickel compounds.[30] The carcinogenic activity of metal ions has only recently received serious attention[31] and could play an important role in the regulation of our environmental health conditions. For example, metal catalysts are sometimes added to commercial commodities. In one case, however, the use of chromium was discontinued when it was learned that it is carcinogenic in laboratory animals.[30]

3 Cancer Chemotherapy[32]

Cancer chemotherapy made its initial defined thrust in 1941 when Huggins and Hodges reported that the sex hormone oestrogen is useful in the treatment of prostatic cancer in men. Later, wartime research on chemical warfare agents led to the discovery of the destruction of white blood cells by nitrogen mustards and hence the potential antileukaemic action of these compounds. In 1948, Farber and associates noticed that folic acid treatment of anaemic children with acute leukaemia led to a worsened leukaemic condition. This suggested the use of antifolic acid compounds for treatment of leukaemia. The first one tried was

[25] A. K. Brewer, *Amer. Scientist*, 1968, **56**, 254.
[26] D. C. Neckers, *J. Chem. Educ.*, 1973, **50**, 164.
[27] J. T. Chan and H. S. Black, *Science*, 1974, **186**, 1216.
[28] V. N. Nigam and A. Cantero, *Adv. Cancer Res.*, 1972, **16**, 1.
[29] H. I. Hadler, *Medikon*, in press; H. I. Hadler and B. G. Daniel, *Cancer Res.*, 1972, **32**, 1037.
[30] A. Furst, Chemical Seminar, California State University, Los Angeles, Oct. 15, 1974.
[31] D. R. Williams, *Chem. Rev.*, 1972, **72**, 203; A. Furst and R. T. Haro, *Progr. Exp. Tumor Res.*, 1969, **12**, 102.
[32] 'Cancer Medicine', ed. J. F. Holland and E. Frei, jun., Lea and Febiger, Philadelphia, 1973.

aminopterin (26a) which was too toxic, but several changes led to MTX (26b). MTX was strikingly effective, not only in acute childhood leukaemia but also against the rare uterine cancer, choriocarcinoma. Prior to this time, five of every six women diagnosed to have this or a related type of cancer died within a year. By 1961, 44 percent of such patients treated with MTX were completely cured from all evidence of cancer and by 1971 MTX and other drugs had raised this recovery rate to 95 percent, some patients being without symptoms for more than five years. In 1947, children with acute leukaemia had only two to four months life expectancy but by 1973 over half of such patients could expect at least a five-year survival.

There are now about 45 anticancer drugs in medical practice on the official list of the National Cancer Institute with about 40 more in, or close to, clinical trials.[33] These antitumour agents can be placed in four classes which are discussed below: (i) alkylating agents, (ii) antimetabolites, (iii) antibiotics, and (iv) miscellaneous.

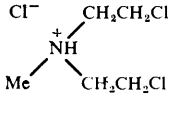
A number of differences have been observed between cancer and normal cells; *e.g.* compared with normal cells, cancer cells have:

lower pH,[34]
greater free-radical character,[35]
tumour-produced hormone peptides,[36]
tumour-associated antigens,[36]
lower calcium ion and higher potassium ion concentrations,[37]
different potassium isotope ratios,[37]
elevated amounts of methylated nucleosides,[38]
higher concentration of plasma mucoproteins[39] and mucopolysaccharides,[28]
greater need of exogenous zinc,[40]
higher biowater content,[41]
and some types (leukaemia cells) need exogenous L-asparagine.[42]

However, these differences are of more use in detecting cancer cells than in being therapeutically exploitable. Most drugs in current use inhibit cell division by interfering in one way or another with the synthesis or use of nucleic acids, or in a few cases during mitoses.[43]

[33] 'Report of the Division of Cancer Treatment', National Cancer Institute, Bethesda, Md., 1974, Vols. 1 and 2.
[34] Z. B. Papanastassiou, R. J. Bruni, E. White, and P. L. Levins, *J. Medicin. Chem.*, 1966, 9, 725; P. Weiss and B. I. H. Scott, *Proc. Nat. Acad. Sci. U.S.A.*, 1963, **50**, 330.
[35] R. A. Passwater, *Amer. Laboratory*, 1973, **5**(6), 10; H. M. Swartz, *Adv. Cancer Res.*, 1972, **15**, 227.
[36] *cf.* T. H. Maugh, jun., *Science*, 1974, **184**, 147.
[37] A. K. Brewer, *Amer. Laboratory*, 1973, **5**(11), 12.
[38] C. C. Cheng, *J. Pharm. Sci.*, 1972, **61**, 645.
[39] D. W. Dixon, *Cancer*, 1973, **31**, 596.
[40] C. P. Li, 'Anticancer Agents Recently Developed in the People's Republic of China', D.H.E.W. Publn. No. (NIH) 74-441, Washington, D.C., 1974.
[41] B. D. Allan and R. L. Norman, *Cancer Chemotherapy Reports Part 1*, 1974, **58**, 296.
[42] C. Tan, *Hosp. Pract.*, 1972, **7**(7), 99.
[43] R. W. Brockman, *Cancer Chemotherapy Reports Part* 2, 1974, **4**(1), 115; V. H. Bono, jun., *ibid.*, p. 131.

A. Alkylating Agents.—Alkylating drugs include nitrogen mustard (7), cyclophosphamide (Cytoxan or CTX) (8), busulphan (9), L-Pam (melphalan or Sarcolysin) (10), cyclohexylchloroethylnitrosoureas (CCNU) (11), streptozotocin (12), prospidin (13), and dipin (14) [(13) and (14) are drugs synthesized in the



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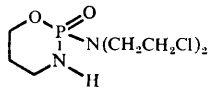

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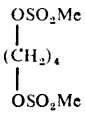

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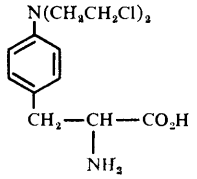
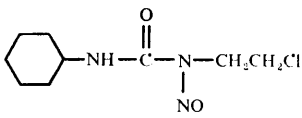
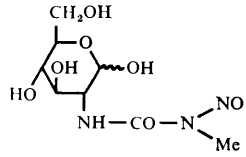


(10)



(11)



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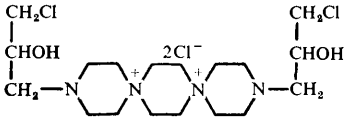

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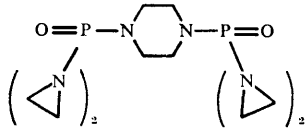
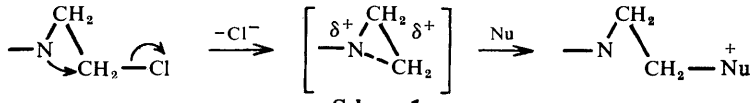


(14)

U.S.S.R.]. Many contain a nitrogen mustard, aziridine, or methanesulphonate group.[44] The alkylating agents react with the nucleophilic hydroxy-, amino-, mercapto-, or imidazole groups of proteins and nucleic acids. However, there is little correlation between their *in vitro* alkylation activities toward 4-(*p*-nitrobenzyl)pyridine, which is often used to assess the alkylating activity of a substance,[45] and their cytotoxicity. In one study, the combined alkylating plus carbamoylating activity correlated with the therapeutic index of a series of drugs.[46] Sulphur mustards are rarely active and simple substitution of phosphorus for nitrogen is ineffective. The length of the chain is important, probably owing to a neighbouring group effect (shown in Scheme 1), and, indeed, several drugs

[44] T. J. Bardos, Z. F. Chielewicz, and P. Hebborn, *Ann. New York Acad. Sci.*, 1969, **163**, 1006.
[45] J. Epstein, R. W. Rosenthal, and R. J. Ess, *Analyt. Chem.*, 1955, **27**, 1435.
[46] G. P. Wheeler, B. J. Bowdon, and J. A. Grimsley, *Proc. Amer. Assoc. Cancer Res.*, 1973 **14**, 26.

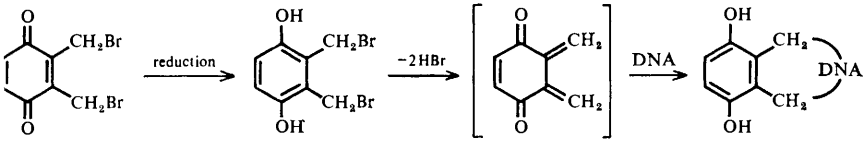


Scheme 1

contain the aziridine ring. Vinylsulphones are ineffective as antitumour agents.[47] Simple alkylating agents react indiscriminately with cellular nucleophiles and consequently have limited therapeutic indexes. Some of the cytotoxic natural products appear to exert their cytotoxic activity *via* alkylations, particularly thiol groups.[48] It is thought that their special stereochemical and molecular structures make them more specific in their alkylation reactions and that they should lead to more effective drugs.

The nitroso-ureas and guanidines have a broad spectrum of antitumour activity;[49] *e.g.*, CCNU (11) cyclohexylcarbamoylates lysine residues of proteins and alkylates nucleic acids: this dual reactivity might explain its broad cytotoxicity against tumours which are resistant to conventional alkylating agents.[50] The *N*-nitroso-amides are being studied for possible brain tumour treatment[51] because of their ability to cross the blood–brain barrier.

Certain benzo- and naphtho-quinone derivatives may undergo bioreduction to cytotoxic alkylating agents (Scheme 2).[52] None of these compounds has yet reached the clinical stage.

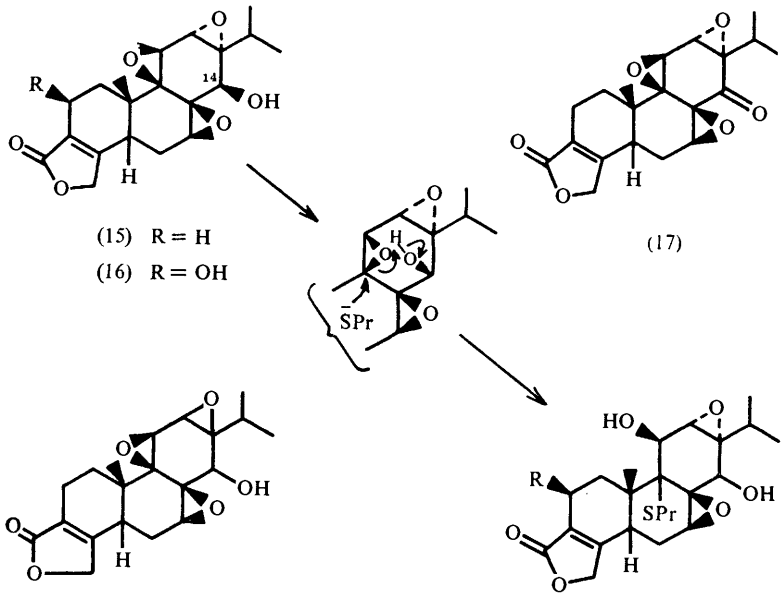


Scheme 2

Quite a number of γ-lactone sesquiterpenes have shown antitumour activity but significant cytotoxicity is dependent upon the presence of an α-methylene group.[53] Cysteine adds readily to these sesquiterpenes and the rates of addition are enhanced when there is a hydroxy or acyl group adjacent to the methylene group. On the other hand, the highly active antileukaemic (toward L-1210 in mice) plant extracts triptolide (15) and tripdiolide (16) appear to alkylate thiols

[47] R. I. Polkina and A. L. Remizov, *Cancer Chemotherapy Abs.*, 1973, **14**(10), 637.
[48] S. M. Kupchan, Symposium on Antibiotics and Neoplasia, 13th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., Sept. 1973; *Fed. Proc.*, in press.
[49] F. M. Schabel, jun., *Cancer Chemotherapy Reports*, 1973, **4**(3), 3; S. K. Carter, *ibid.*, p. 35.
[50] C. J. Cheng, S. Fujimura, D. Grunberger, and I. B. Weinstein, *Cancer Res.*, 1972, **32**, 22.
[51] L. E. Broder and D. P. Rall, *Progr. Exp. Tumor Res.*, 1972, **17**, 373.
[52] A. J. Lin, C. W. Shansky, and A. C. Sartorelli, *J. Medicin. Chem.*, 1974, **17**, 558.
[53] G. A. Howie, P. E. Manni, and J. M. Cassady, *J. Medicin. Chem.*, in press; S. M. Kupchan, M. A. Sakin, and A. M. Thomas, *J. Medicin. Chem.*, 1971, **14**, 1147; K.-H. Lee, E.-S. Huang, C. Piantadosi, J. S. Pagano, and T. A. Geissman, *Cancer Res.*, 1971, **31**, 1649; K.-H. Lee, S.-H. Kim, H. Furukawa, and C. Piantadosi, *J. Medicin. Chem.*, 1975, **18**, 59.

by epoxide ring opening and the process is assisted by the 14-hydroxy-group.[54] Thus, the ketone (17) and α-oriented 14-hydroxy-isomer (18) are cytotoxic against KB cells in culture but inactive *in vivo* against L-1210. The strong intra-

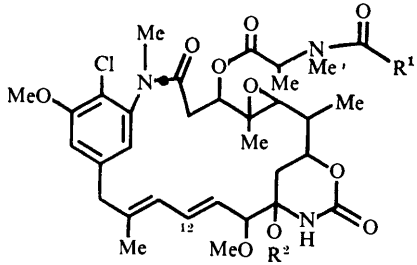


(15) R = H
(16) R = OH

(17)

(18)

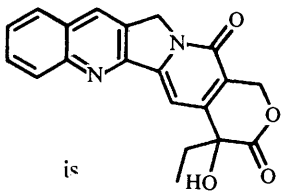
molecular H-bond in (15) and (16) is revealed by n.m.r. spectroscopy. Similarly, maytansine (19) is an anticancer drug (in clinical trials) which exhibits powerful antileukaemic action whereas its methyl ether (20) shows no antileukaemic activity (although it is cytotoxic *in vitro*).[55]



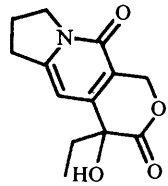
(19) R^1 = Me ; R^2 = H
(20) R^1 = Me ; R^2 = Et

[54] S. M. Kupchan and R. M. Schubert, *Science*, 1974, **185**, 791.
[55] S. M. Kupchan, Y. Komoda, A. R. Branfman, R. G. Dailey, jun., and V. A. Zimmerly, *J. Amer. Chem. Soc.*, 1974, **96**, 3706.

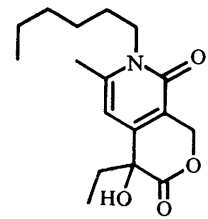
Several attempts have been made to identify the portion of the camptothecin drug molecule (21) responsible for its oncolytic property.[56] Not only is the α-hydroxy-lactone portion necessary for antitumour activity but also the A and B rings appear to be crucial to activity, since fragments (I) and (II) have no useful activity.[57]



(21)



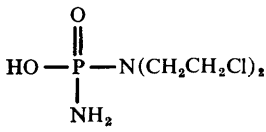
(I)



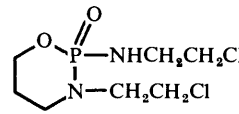
(II)

Considerable effort has been expended toward an identification of the cytotoxic active metabolite of cyclophosphamide (CTX) (8).[58] Recent work has shown that an early step in its activation involves C-4 hydroxylation of the oxazaphosphorine ring.[59] Indeed, the 4-peroxycyclophosphamide has been isolated.[60] It is stable and cytotoxic *in vitro* as well as *in vivo* in L-1210. A later metabolite is *NN*-bis(chloroethyl)phosphoradiamidic acid (22), which is itself a potent cytotoxic agent *in vivo* with antitumour effects resembling those of its precursor, CTX.[61] Although isophosphamide (23) is more cytotoxic than CTX in preclinical studies, it offers no useful increased antitumour effect in clinical trials.[62]

One rationale of designing a more effective drug is to attach the nitrogen



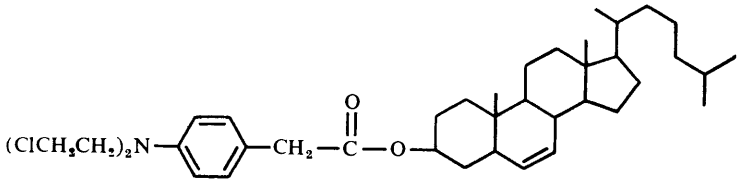
(22)



(23)

[56] M. Shamma and V. St. Georgiev, *J. Pharm. Sci.*, 1974, **63**, 163; A. G. Schultz, *Chem. Rev.*, 1973, **73**, 385.
[57] S. Danishefsky, J. Quick, and S. B. Horwitz, *Tetrahedron Letters*, 1973, 2525; S. Danishefsky and J. Etheredge, *J. Org. Chem.*, 1974, **39**, 3430.
[58] N. E. Sladek, *Cancer Res.*, 1973, **33**, 651.
[59] A. Takamizawa, S. Matsumoto, T. Iwata, K. Katagiri, Y. Tochino, and K. Yamaguchi, *J. Amer. Chem. Soc.*, 1973, **95**, 985.
[60] R. F. Struck, *J. Amer. Chem. Soc.*, 1974, **96**, 313.
[61] M. Colvin, C. A. Padgett, and C. Fenselau, *Cancer Res.*, 1973, **33**, 915.
[62] D. L. Ahmann, H. F. Bisel, and R. G. Hahn, *Cancer Chemotherapy Reports, Part 1*, 1974, **58**(6), 861; D. N. Bremmer, J. St.C. McCormick, and J. W. W. Thomson, *ibid.*, p. 889.

mustard moiety on to a biological carrier such as a polypeptide, carbohydrate, nucleoside, or even a tumour-specific antibody,[63] which would deliver the drug to the tumour site. For instance, the cholesterol ester phenesterin (24) is at



(24)

least as effective as CTX and more potent than chlorambucil.[64] However, a recent survey of steroid mustards has revealed that very few are effective antitumour agents.[65] The Japanese were the first to make use of an amino-acid carrier, such as the phenylalanine mustard, L-Pam (10). The original notion in synthesizing L-Pam was that it might exhibit selective cytotoxic action against melanoma cells, which utilize phenylalanine in melanin synthesis. Although this expectation did not materialize (it is inferior to CTX), L-Pam is the drug of choice against multiple myeloma (diffuse cancer in bone marrow). The Chinese have found the *N*-formyl derivative (N-F) of L-Pam to be less toxic and to have a higher therapeutic index.[40] Among the many ring-substituted analogues of N-F synthesized and tested, the *o*-methoxy-derivative is the most effective. The Russians have developed promising drugs of this type with a tetrapeptide or pentapeptide chain attached. Usually, but not always, the L-amino-acid units are more active than the D-isomers.

A considerable number of analogues of Streptozotocin (12) have been prepared, mostly with structural modifications of the sugar moiety. Generally, differences in their antitumour activity are not large, which suggests that the sugar fragment is functioning as a non-specific hydrophilic carrier for the *N*-methyl-*N*-nitrosourea group.[66] Replacement of the methyl group in Streptozotocin by CH_2CH_2Cl gives a more active agent against leukaemic L1210 in mice. The compound is undergoing pharmacological evaluation preliminary to clinical trials.[66a]

Some metals are involved in chemical carcinogenesis whereas others are connected with therapy. In fact, one of the most potent, broad-spectrum antitumour agents yet developed is a metal complex, *cis*-dichlorodiammineplatinum (44).[67] It is noteworthy that both the *cis*- and the *trans*-isomers bind to DNA

[63] J. H. Linford, G. Froese, I. Berczi, and L. G. Iraels, *J. Nat. Cancer. Inst.*, 1974, **52**, 1665.
[64] E. B. Feldman, H. Paul, and R. Cheron, *Cancer Chemotherapy Reports Part 1*, 1972, **56**, 1.
[65] J. B. Jones, D. J. Adam, and J. D. Leman, *J. Medicin. Chem.*, 1971, **14**, 827.
[66] A. N. Fujiwara, E. M. Acton, and D. W. Henry, *J. Medicin. Chem.*, 1974, **17**, 392.
[66a] T. P. Johnston, G. S. McCaleb, and J. A. Montgomery, *J. Medicin. Chem.*, 1975, **18**, 104.
[67] B. Rosenberg, *Naturwiss.*, 1973, **60**, 399.

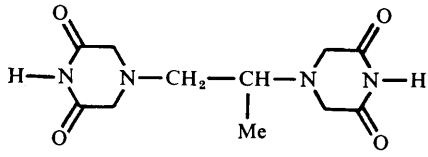
but only the *cis*.isomer forms interstrand cross links and is cytotoxic.[68] Spectral measurements indicate that the *cis*-isomer binds at either N-1 and 6-NH_2 or N-7 and 6-NH_2 of adenosine and cytidine.[69] A wide variety of platinum(II) complexes have been investigated, and although *cis*-$Pt(NH_3)_2Cl_2$ is well along in clinical trials, there are several analogues found to be more potent and less toxic in *in vivo* and *in vitro* tests. One of these is the cyclohexylamine complex[70] and another is a group of pyrimidine complexes.[71] In contrast to the strongly cytotoxic platinum complexes, palladium analogues have little activity.[72] The mainland Chinese have developed antimony complexes of EDTA which have some therapeutic use.[40] The activity of these compounds appears to depend on their ability to inhibit the incorporation of zinc into tumour cells. Gallium (citrate) is another metal which preferentially localizes in certain human tumours and, indeed, gallium nitrate has reached the stage of clinical trials.[73]

Residual protein bound to DNA contains sulphydryl groups which could be the site of electrophilic attack or free-radical attack of carcinogens. In any event, such protein has excess negative charge. Anti-neoplastic agents have been prepared by placing the sulphydryl-inhibiting group three carbon atoms from a cationic centre, supposedly complementing the structure of the DNA-bound protein.[74] Arsenic and mercury compounds act as sulphydryl inhibitors and sometimes preferentially attack cancer cells.[75]

Many studies have been made on the cytotoxic activity of copper chelates.[76] There is a significant correlation between the antitumour activity of a group of heterocyclic aldehyde thiosemicarbazones in animal systems and their metal chelating properties.[77] These compounds are thought to exert their antitumour activity by inhibition of DNA synthesis at the level of the enzyme, ribonucleoside diphosphate reductase, presumably by chelation of the iron moiety of the enzyme molecule. There is a relationship between serum copper level and disease activity in patients with Hodgkin's disease.[78]

[68] J. J. Roberts and J. M. Pascoe, *Nature*, 1972, **235**, 283; M. Slavik and S. K. Carter, *Cancer Chemotherapy Reports Part 3*, 1973, **4**(2), 265.
[69] S. Mansy, B. Rosenberg, and A. J. Thomson, *J. Amer. Chem. Soc.*, 1973, **95**, 1633; R. M. Izatt, J. J. Christensen, and J. H. Rytting, *Chem. Rev.*, 1971, **71**, 439; U. Weser, *Structure and Bonding*, 1968, **5**, 42.
[70] T. A. Connors, M. Jones, W. C. J. Ross, P. D. Braddock, A. R. Khokhar, and M. L. Tobe, *Chem.–Biol. Interactions*, 1972, **5**, 415.
[71] J. P. Davidson, P. J. Paula, R. G. Fischer, jun., S. Mansy, H. J. Peresie, B. Rosenberg, and L. VanCamp, *Cancer Chemotherapy Reports*, in press.
[72] M. J. Cleare and J. D. Hoeschele, *Bioinorg. Chem.*, 1973, **2**, 187.
[73] M. M. Hart, R. H. Adamson, and V. T. Oliverio, *Proc. Amer. Assoc. Cancer Res.*, 1971, 12, 81; *J. Nat. Cancer Inst.*, 1971, **47**, 1121.
[74] F. E. Knock, Abstracts of the 150th meeting, American Chemical Society, 1965, 6-P.
[75] F. E. Knock, 'Anticancer Agents', Thomas, Springfield, Illinois, 1967.
[76] E. A. Coates, G. Holbein, J. McDonald, R. Reed, and H. G. Petering, Abstracts, Division of Medicinal Chemistry, American Chemical Society National Meeting, Los Angeles, April, 1974.
[77] I. H. Krakoff, E. Etcubanas, C. Tan, K. Mayer, V. Tethune, and J. H. Burchenal, *Cancer Chemotherapy Reports, Part 1*, 1974, **58**(2), 207; F. A. French, E. J. Blanz, jun., S. C. Shaddix, and R. W. Brockman, *J. Medicin. Chem.*, 1974, **17**, 172; K. C. Agrawal, A. J. Lin, B. A. Booth, J. R. Wheaton, and A. C. Sartorelli, *J. Medicin. Chem.*, 1974, **17**, 631.
[78] C. F. Tessmer, M. Hrgovcic, and J. Wilbur, *Cancer*, 1973, **31**, 303, 1337.

The process of chelation is also intimately involved in the role of metals in metallochemotherapy.[79] For example, some drugs have increased activity when administered as metal complexes[31] and a number of metal chelates inhibit tumour growth.[80] Pre-administration of the chelating agent EDTA or the di-imide ICRF-159 (25) prevents increase coronary perfusion pressure induced by



(25)

the drugs Daunomycin (37) or Adriamycin (38), two effective drugs with high cardiac toxicity. It is speculated that the chelating agents reduce the concentrations of certain metabolites of the drugs by removing cations needed for formation of the metabolites and thereby reduce the toxicities.[81] Thus, chelates may be cytotoxic by reacting directly with cellular components or they may be involved by serving as metal transport systems to get metal ions into the cell.

B. Antimetabolites.—Antimetabolites are substances mistakenly incorporated by a cell and, when inside, these 'look alike' antagonists interfere with the normal activities of the cell. Various substances are needed by the cell to form nucleic acids for proliferation. Tetrahydrofolic acid plays a key role in the synthesis of purines and thymidylate and thus is a vital cofactor for nucleic acid synthesis and cellular replication. Because interference with foliate metabolism can influence cell growth, compounds which affect foliate metabolism inhibit the growth of bacteria, protozoa, and neoplastic cells and suppress the immune responses. In this connection, many purines and nucleosides have antitumour properties. Some of the antimetabolite cancer drugs in use [(26)—(31)] and the corresponding nucleic acid precursors are shown in Figure 6.

MTX (26a) has been used for more than 20 years against a wide variety of malignancies.[82] Although many structure–activity studies have been made on the pteroyl-glutamic acid system,[83] MTX is still the single drug of choice for

[79] A. Furst, 'Chemistry of Chelation in Cancer', Thomas, Springfield, Illinois, 1963.
[80] F. P. Dwyer, E. Mayhew, E. M. F. Roe, and A. Shulman, *Brit. J. Cancer*, 1965, **19**, 195.
[81] E. H. Herman, R. M. Mhatre, I. P. Lee, and V. S. Waravdekar, *Proc. Soc. Exp. Biol. Med.*, 1972, **140**(1), 234.
[82] R. B. Livingston and S. K. Carter, 'Single Agents in Cancer Chemotherapy', Plenum Press, New York, 1970.
[83] J. A. R. Mead, H. B. Wood, jun., and A. Goldin, *Cancer Chemotherapy Reports, Part 2*, 1968, **1**, 273; J. R. Bertino, *Ann. New York Acad. Sci.*, 1971, **196**, 7-519; E. C. Roberts and Y. F. Shealy, *J. Medicin. Chem.*, 1974, **17**, 219.

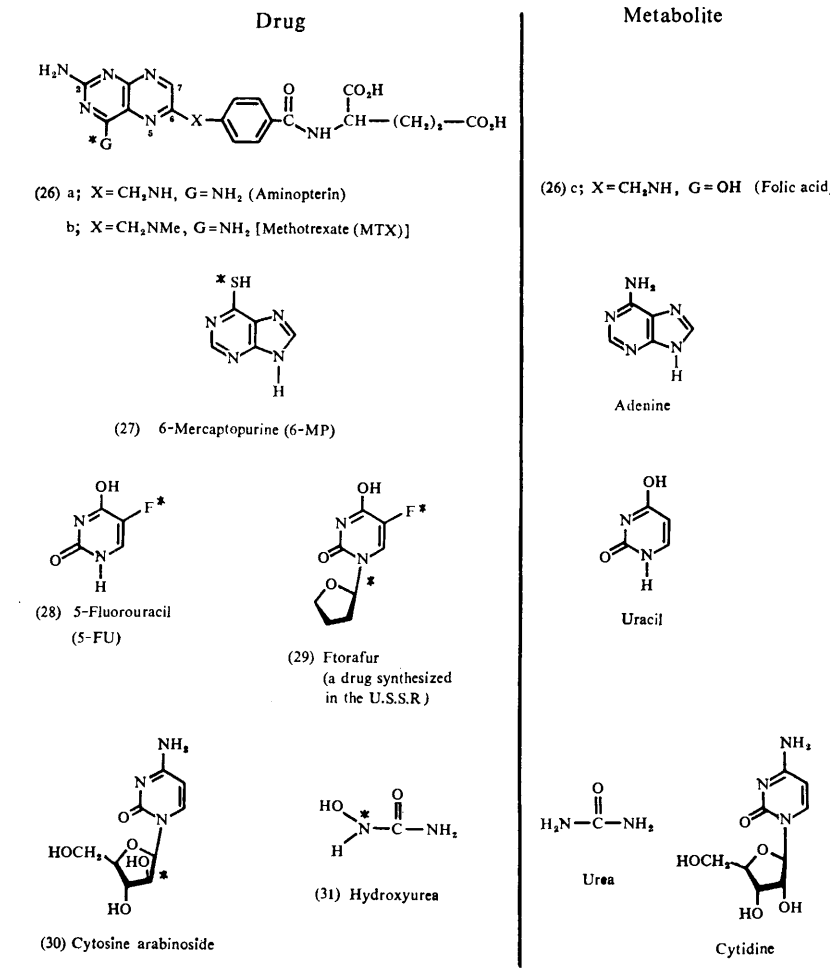
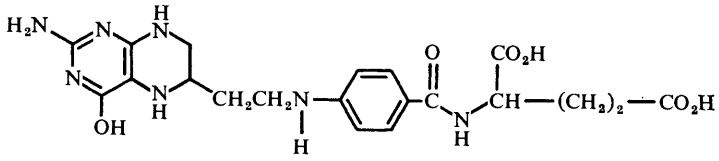


Figure 6 *Some antimetabolite cancer drugs and their metabolite analogues. *Sites of structural differences*

meningeal leukaemia.[84] Some generalizations on the effects of structural changes on antitumour activity for the folic acid congeners are:

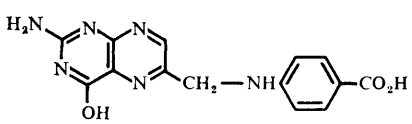
(i) significant activity is found only when there is a free 4-NH_2 group, with the exception of 5,6,7,8-tetrahydrohomofolic acid (32) and its 5-Me derivative;

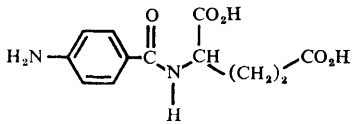
[84] L. E. Broder and S. K. Carter, 'Meningeal Leukemia', Plenum Press, New York, 1972; J. H. Burchenal and M. R. Dollinger, in 'Chemotherapy of Cancer', ed. W. H. Cole, Lea and Febiger, Philadelphia, 1970, p. 75.

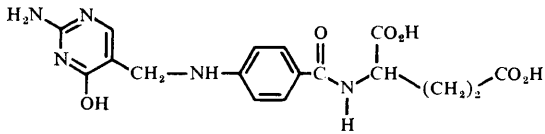


(32)

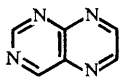
(ii) introduction of halogen into the benzene ring of MTX increases activity;
(iii) fragments of the folic acid molecule shown in Figure 7 have little or no antitumour activity;







Of 61 tested, only a small number active.



Of 140 tested, none active.

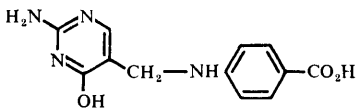


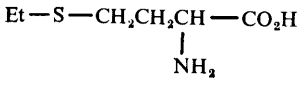
Figure 7

(iv) modifications of the glutamic acid moiety does not increase antileukaemic activity;
(v) lipid-soluble dialkyl esters of MTX offer additional promise for the treatment of meningeal leukaemia in man because of their ability to cross the blood–brain barrier;[85]
(vi) the 1- and 3-deaza-analogues of MTX and their dihydro-derivatives,[86] as

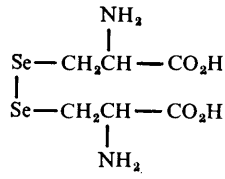
[85] D. G. Johns, D. Farquhar, M. K. Wolpert, B. A. Chabner, and T. L. Loo, *Drug Metabolism and Disposition*, 1973, **1**, 580.
[86] R. D. Elliott, C. Temple, jun., and J. A. Montgomery, *J. Medicin. Chem.*, 1974, **17**, 553.

well as homofolic acid [(26d); X = CH_2CH_2NH, G = OH] and isofolic acid [(26e); X = $NHCH_2$, G = OH][87] retain some activity.

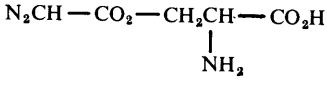
6-Mercaptopurine (27) is the most extensively used of the purine antagonists.[88] 5-FU (28) is the most effective single agent for the treatment of cancer of the colon,[89] or rectum, but is inferior to CTX (8) against lung cancer.[82] Hydroxyurea (31) is a highly selective inhibitor of DNA synthesis by interfering with the enzyme that reduces ribonucleotides to deoxyribonucleotides. Hydroxyurea may also act as a radiosensitizer in brain tumours and preliminary trials in its use with radiotherapy have given some very encouraging results.[90] Many amino-acid antagonists (*i.e.* compounds which act to inhibit the incorporation of amino-acids in purine biosynthesis) such as ethionine (33), selenium cystine (34), or azaserine (35), are extremely toxic and are not useful in clinical cancer chemotherapy. The amino-acid derivative, *S*-trityl-L-cysteine (36) is active against leukaemia L-1210, and apparently the zwitterion form is important for activity.[91]



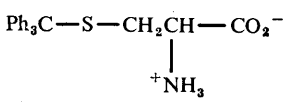
(33)



(34)



(35)



(36)

Since fluorine imparts antitumour activity to some pyrimidines, there is the notion that the same result might occur with amino-acids. Accordingly, some mainland Chinese prepared a series of fluorine-containing amino-acids, some of which exhibit *in vivo* antitumour activity.[40]

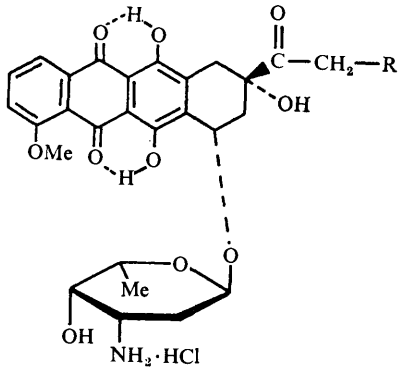
A wide variety of nucleoside analogues are being synthesized and tested for

[87] M. G. Nair and C. M. Baugh, *J. Medicin. Chem.*, 1974, **17**, 223.
[88] On structure–activity, see: A. Goldin, H. B. Wood, jun., and R. R. Engle, *Cancer Chemotherapy Reports, Part 2*, 1968, **1**, 1.
[89] M. Slavik and S. K. Carter, *Cancer Chemotherapy Reports Part 3*, 1973, **4**(2), 265.
[90] L. E. Broder and D. P. Rall, *Progr. Exp. Tumor Res.*, 1972, **17**, 363.
[91] K. Y. Zee-Cheng and C. C. Cheng, *J. Medicin. Chem.*, 1972, **15**, 13.

their cytotoxicity. Among the structural modifications are use of different purines and heterocyclic bases, their combination with different sugars, formation of *C*-nucleosides,[92] and oligomers.[93] Various groups have been substituted into purine molecules, and deazapurines (carbon in place of a nitrogen atom) and azapurines (nitrogen for carbon) have been used.[94] Sugar fragments, such as β-ribose, β-arabinose, or α-xylose, have been modified with sulphur or selenium in place of oxygen atoms and alternatively converted into the respective alkyl ethers or phosphate esters.[94,95]

C. Antibiotics.—There are several very effective antibiotic cancer drugs. These compounds may act at various points in the sequence of DNA to RNA to protein but most bind to the DNA molecule and inhibit the production of DNA-dependent RNA. A few inhibit RNA-dependent DNA polymerase (reverse transcriptase).[96] In some cases, the DNA–drug complex has greater antitumour activity than the drug alone.[97]

Currently there is intense international interest in a drug synthesized in Italy, Adriamycin (38).[98] It has the widest spectrum of clinical activity of any known compound.[99] Adriamycin is much more effective than Daunomycin (37). The



(37) R = H

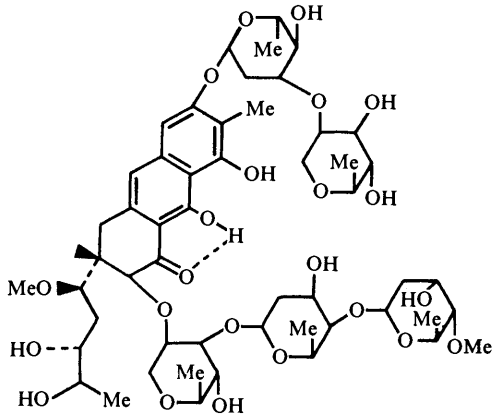
(38) R = OH

[92] E. M. Acton, K. J. Ryan, D. W. Henry, and L. Goodman, *Chem. Comm.*, 1971, 986.
[93] S. A. Hiller, U.S.–U.S.S.R. Joint Meeting on Treatment of Lung Cancer, Institute Experimental and Clinical Oncology, Moscow, March, 1974.
[94] J. A. Montgomery, A. K. Shortnacy, and H. J. Thomas, *J. Medicin. Chem.*, in press.
[95] W. W. Lee, A. P. Martinez, L. Goodman, and D. W. Henry, *J. Org. Chem.*, 1972, **37**, 2923; *J. Medicin. Chem.*, 1973, **16**, 570; N. Ototani and R. L. Whistler, *ibid.*, 1974, **17**, 535; G. H. Milne and L. B. Townsend, *ibid.*, 1974, **17**, 263.
[96] *Cf.* R. D. Johnson, A. Haber, and K. L. Rinehart, jun., *J. Amer. Chem. Soc.*, 1974, **96**, 3316.
[97] D. W. Henry, *Cancer Chemotherapy Reports Part 2*, 1974, **4**(4), 1974.
[98] F. Arcamone, G. Cassinelli, G. Franceschi, R. Mondelli, P. Grezzi, and S. Penco, *Gazzetta*, 1970, **100**, 949.
[99] S. Perry, *Cancer Chemotherapy Reports Part 1*, 1974, **58**(1), 117.

fact that this change in activity can be brought about by merely replacing a hydrogen atom by a hydroxy-group in this large molecule lends hope that other molecular changes can further improve the therapeutic index. However, simple chemical derivatives, such as esterification of the hydroxy-groups or Schiff base carbonyl derivatives of the ketone, are not markedly more effective.[100]

The quinone structure occurs in several natural product anticancer drugs. The structure–antitumour activity relationships of over 1500 quinones have been summarized recently.[101] The aziridinyl quinones are of special interest because of their CNS anti-neoplastic activity.

There is great hope in the Soviet Union for Variomycin A (39), a drug synthesized in the U.S.S.R. Both drugs, Adriamycin and Variomycin A, form complexes with DNA *in vitro* and are believed to do so *in vivo*.

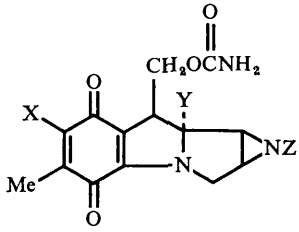


(39)

Extensive structure–activity studies of the mitomycin structure (40) have been made, particularly with changes at X, Y, and Z.[102] Mitomycin C (40a), a drug synthesized in Japan, is shown. These changes alter the toxicity, cytotoxicity, and reduction potential of the quinone, among other properties. Degradative studies have shown that although the aziridine ring is an important contributor to the antitumour activity, it is not an absolute requirement.[103] Also, the

[100] L. Lenaz, A. Necco, T. Dasdia, and A. DiMarco, *Cancer Chemotherapy Reports Part 1*, 1974, **58**(6), 769.
[101] J. S. Driscoll, G. F. Hazard, jun., and H. B. Wood, *Cancer Chemotherapy Reports Part 2*, 1974, **4**(2), 1.
[102] R. Kojima, J. Driscoll, N. Mantl, and A. Goldin, *Cancer Chemotherapy Reports Part 2*, 1972, **3**(1), 121.
[103] T. R. Witty and W. A. Remers, *J. Medicin Chem.*, 1973, **16**, 1280.

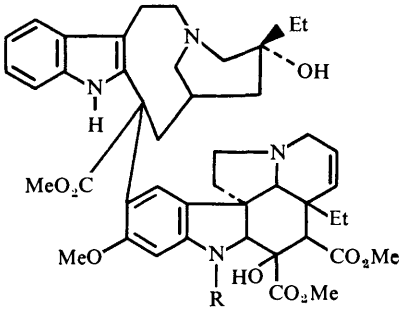
observation that the bioreductive benzoquinone derivatives[103a] mentioned among the alkylating agents are potent inhibitors of DNA and RNA synthesis



(40) a; X = NH_2, Y = OMe, Z = H

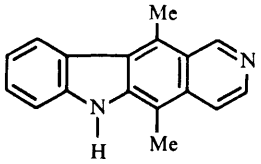
after bioreduction adds further evidence to the claim that the carbamyl group and the aziridine ring of mitomycin C are replaceable without substantial loss of cytotoxic activity.

D. Miscellaneous Agents.—Several miscellaneous antitumour agents are shown in Figure 8.

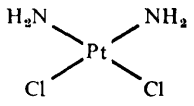


(41) R = Me

(42) R = CHO



(43) Ellipticine



(44) *cis*-Dichlorodiammineplatinum

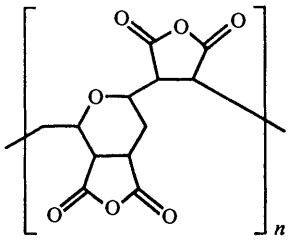
Figure 8

Hormonal compounds are among the oldest of anticancer drugs. Male and female hormones are effective against breast cancer, and female hormones are effective against prostate cancer.

A large number of plant extracts exhibit antitumour activity and two drugs

[103a] A. J. Lin, L. A. Cosby, and A. C. Sartorelli, *Cancer Chemotheapy Reports Part 2*, 1974, 4(4), 23.

from such sources are the antimitotic agents (agents which destroy mitotic spindle, thereby halting cell division) Vinblastine (41) and Vincristine (42), isolated from the periwinkle *Vinca rosea*. An as yet unidentified alkaloid extracted from narcissus bulbs exhibits better antileukaemic activity in mice than several DNA-binding agents (CTX, BCNU, Daunomycin), antimetabolites (MTX, 6-MP, 5-FU), other alkaloids (Vincristine), reverse transcriptase inhibitors (rifamycin), and interferon inducers (poly I:C).[104] That is quite a claim. Pharmaceutical, toxicological, and clinical tests will show what future there is for the alkaloid. A 1:2 copolymer of divinyl ether and maleic anhydride (45)—called DIVEMA by some—is active against several solid tumours and has been approved for clinical trials.[105] The fractions of m.w. in the 2500—15 000 range are less toxic and maintain the activity shown by the heavier cuts of m.w. 45 000. The polymer induces interferon and stimulates the immune response.



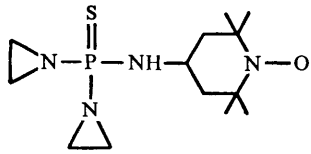
(45)

One of the few antineoplastic agents which exploits a difference between normal and cancer cells is L-asparaginase (L-A). Whereas normal cells can synthesize their own asparagine and are not affected by the presence of L-A, certain leukaemia cells are dependent on exogenous L-asparagine. The enzyme eliminates exogenous L-asparagine *in vivo* and inhibits the growth of the dependent cancer cells. Although the use of L-A in combination chemotherapy has shown superior results, its high toxicity has limited its use so far.[42]

A laboratory in the U.S.S.R. has found that hindered phenols, the free radicals of which are stable because steric hindrance prevents their dimerization,[106] make good anticancer agents and they are undergoing clinical trials.[107] Similarly, in the preclinical stage, the spin-labelled antitumour agent PAT (46) is more effective than the analogue, Thio-TEPA.[107] The observation that carcinogen-induced cancers can be prevented by free-radical scavengers is of wide current interest.[108] The free-radical character of cancer tissue not only provides a potential

[104] N. Suzuki, S. Tani, S. Furusawa, and E. Furusawa, *Proc. Soc. Exp. Biol. Med.*, 1974, **145**, 771.
[105] G. B. Butler, *J. Pure Appl. Chem.*, in press.
[106] L. N. Ferguson, 'Organic Molecular Structure', Willard Grant, Boston, 1975, p. 528.
[107] N. M. Emanuel, Acad. Sci. U.S.S.R., Moscow, Preprint, 1974; See also, G. Sosnovsky, Y.-I. Yeh, and G. Karas, *Z. Naturforsch*, 1973, **28c**, 781.
[108] K. K. Geogrieff, *Science*, 1972, **173**, 537.

avenue for treatment but also offers a possible means of early detection of cancer cells.[108a] There are several isolated bits of circumstantial evidence for



(46)

the free-radical nature of chemical carcinogenesis. For instance, induction of stomach cancer by aromatic hydrocarbons,[109] FAA,[110] or *N*-nitroso-compounds[111] is markedly less in animals fed antioxidants.[35] The urine of heavy smokers with a high incidence of bladder cancer is deficient in vitamin C (a possible protective agent) but high in free radicals and the carcinogen cannabaric acid—presumably a metabolite of tryptophan.[35] The increased electron spin resonance (e.s.r.) signals[112] observed for the plasma of cancer patients has been attributed to the presence of a copper protein ceruloplasmin.[113] Soviet scientists have found an inverse relationship between the level of lipid free radicals and antioxidation activity (A.O.A.) in tumour cells. Agents which reduce the A.O.A. inhibit the growth of tumours.

It has been observed that as solid animal tumours or human leukaemia grow, the e.s.r. signal reaches a peak and then declines. Even in remissions, the free-radical level remains higher than in healthy controls, implying the persistence of latent leukaemic foci. For instance, uranium miners and heavy smokers have high e.s.r. signals for their sputum although regular histological tests fail to reveal the presence of cancer cells. Drugs kill only a fixed percentage of tumour cells. If treatment ceases too soon, the tumour regrows from the remaining cells. Hence it is important to be able to detect cancer cells at a low concentration to know when treatment is needed as well as when it can be stopped.

What is needed is a simple biochemical or physical organic method for the early detection of cancer. Cancerous tissue is diagnosed by histological examination. It is accompanied, however, by certain biological changes, such as those listed on page 295. Accordingly, cancer detection methods are being explored

[108a] Gordon Research Conference on Magnetic Resonance in Biology and Medicine, Tilton, New Hampshire, August 1974.
[109] R. J. Shamberger, *J. Nat. Cancer Inst.*, 1970, **44**(4), 931; *ibid*, 1972, **48**(5), 1491; S. L. Haber and R. W. Wissler, *Proc. Soc. Exp. Biol. Med.*, 1962, **111**, 774; L. W. Wattenberg, *J. Nat. Cancer Inst.*, 1972, **48**(5). 1425.
[110] J. R. Harr, J. H. Exon, P. D. Whanger, and P. H. Weswig, *Clin. Toxicol.*, 1972, **5**(2), 187.
[111] S. S. Mirvish, L. Wallcave, M. Eagen, and P. Shubik, *Science*, 1972, **177**, 65.
[112] Staff report, *Medical World News*, Jan. 12, 1973, p. 20.
[113] C. Mailer, H. M. Swartz, M. Konieczny, S. Ambegaonkar, and V. L. Moore, *Cancer Res.*, 1974, **34**, 637.

which involve, among others, the measurement of these biological constituents* and of potassium isotope ratios[36] and n.m.r. spectroscopy.[114] For instance, the concentration of potassium ions in cancer cells is twice that in normal cells. Water molecules are less rigidly bound and this is reflected in the shapes of the n.m.r. signals. Another experimental technique which offers promise for the detection of solid tumours such as breast, lung, skin, and others, is *thermovision.* Presumably, the greater metabolic rate in tumour cells causes an elevation in tissue temperatures, which can be detected and located by an i.r. scanning instrument.[115]

4 Search for New Drugs

Many antitumour compounds to reach medical practice in the United States came through the mass screening programme of the National Cancer Institute. Thus, the N.C.I.[33] screens 15 000—50 000 substances annually, including compounds submitted by the scientific community, some especially synthesized, fermentation products, extracts of plants (*ca.* 4000 per year) from all over the world,[116] and extracts of marine animals[117,118] and insects.[118] Many cytotoxic substances have been isolated but surprisingly to date no clinically useful antitumour drug has been developed from the sea except cytosine arabinoside.[119] It might be mentioned that clams and seaweed were frequently used for cancer therapy in Chinese traditional medicine.[40] As is to be expected, the specifically synthesized compounds are the most expensive but yield the largest percentage of agents to reach the clinical trial stage.

What is sorely needed is a good guide or rationale for planning the structure of an effective cytotoxic agent. This stage will come when we have an understanding of the mechanisms of action of antitumour drugs, which in turn is fostered by having a working hypothesis for the mode of action of a given type of drug. Organic chemists can play a leading role here. From their experience in probing reaction mechanisms *in vitro*, they can postulate likely intermediate metabolites and design experiments to follow the reaction sequences of drugs.

* Related to this, Hoffmann–LaRoche sells a kit to measure traces of carcinoembryonic antigen (C.E.A.) in blood plasma. Abnormally high levels of C.E.A. have been linked to cancer of the colon, lung, rectum, and other organs. However, the tests are often false and need to be used in conjunction with other diagnostic methods.

[114] I. D. Weisman, L. H. Bennett, L. R. Maxwell, jun., M. W. Woods, and D. Burk, *Science*, 1972, **178**, 1288; R. Damadian, *Science*, 1971, **171**, 1151; A. K. Brewer, *Amer. Laboratory*, 1973, **5**(11), 12; C. F. Hazlewood, D. C. Chang, and D. Medina, *Proc. Nat. Acad. Sci.*, 1972, **69**, 1478.

[115] 'Thermovision in Medicine', ed. G. D. Shushkov and M. M. Miroshnikov, Leningrad, 1972; see N.I.H. Library Translation, N.I.H.-74-418C.

[116] S. M. Kupchan, Y. Komoda, A. R. Branfman, R. G. Dailey, jun., and V. A. Zimmerley, *J. Amer. Chem. Soc.*, 1974, **96**, 3706; S. M. Kupchan, T. Fujita, M. Maruyama, and R. W. Britton, *J. Org. Chem.*, 1973, **38**, 1260; M. C. Wani, H. L. Taylor, and M. E. Wall, *J.C.S. Chem. Comm.*, 1973, 390.

[117] R. J. Quinn, M. Kashiwagi, R. E. Moore, and T. R. Norton, *J. Pharm. Sci.*, 1974, **63**, 257.

[118] G. R. Pettit, R. H. Ode, and T. E. Harvey, tert., *Lloydia*, in press.

[119] C. P. Li, A. Goldin, and J. L. Hartwell, *Cancer Chemotherapy Reports Part 2*, 1974, **4**(3), 97.

Some of the approaches used presently as guidelines in searching for potential antitumour agents are described below.

A. Quantitative Structure–Activity Relationships (Q.S.A.R.)—Several techniques have been developed for the strategic design of molecules with maximum bioactivity. There are two general approaches used: ranking substructure contributions to biological activity by statistical methods, and correlating physiochemical properties of a family of molecules with their bioactivity. In the first group are the pattern recognition method[120] and molecular orbital[121] and quantum chemical treatments,[122] while in the latter category are the widely used Hansch method[123] and Free–Wilson model.[124]

Extensive use has been made of linear free energy equations in recent years to correlate the bioactivity of chemicals. The general procedure is to take a biologically active compound and study the effects of structural changes on its activity, directed toward finding the substitution pattern of the derivative expected to be the most potent. In the Hansch approach, an equation is used of the type

$$\log \frac{1}{C_s} = k_1\pi + k_2\sigma + k_3E_s + k_4$$

where C_s = the concentration of member s which gives a standard response, *e.g.* LD_{50}, I_{50}, *etc.*;

π = hydrophobic substituent constants (determined from distribution coefficients of model compounds between n-octanol and water), which reflect lipophilic character of substituents;

σ = Hammett substituent constants, which reflect electronic effects of substituents;

E_s = Taft steric constants, which reflect spatial requirements of groups.

k_1, k_2, k_3, and k_4 are constants, determined by multiple regression analysis. The substituent constants are available in tables for many common groups.

The rationale is that the bioactivity of a drug is determined by a summation of its hydrophobic–lipophilic character, its charge distribution, and its molecular shape. By choosing the proper substituent changes, guided by the use of the equation above, attempts are made to predict the structure of the most effective

[120] B. R. Kowalski and C. F. Bender, *J. Amer. Chem. Soc.*, 1974, **96**, 916; R. D. Cramer, tert., G. Redl, and C. E. Berkoff, *J. Medicin. Chem.*, 1974, **17**, 533.

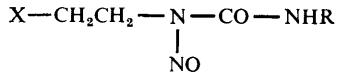
[121] L. B. Kier, 'Molecular Orbital Theory in Drug Research', Academic Press, New York, 1971; A. J. Wohl, 'Drug Design', Vol. 1, ed. E. J. Ariens, Academic Press, New York, 1971, p. 391.

[122] T. K. Lin, *J. Medicin. Chem.*, 1974, 17, 151; J.-L. Montero, J. L. Imbach, R. E. Christoffersen, D. Spangler, G. G. Hall, and G. M. Maggiora, *J. Amer. Chem. Soc.*, 1973, **95**, 8526.

[123] Two recent reviews are: (*a*) A. Verloop, in 'Drug Design', Vol 3, ed. E. J. Ariens, Academic Press, New York, 1972, Chap. 2; (*b*) Biological Correlations—The Hansch Approach', ed. R. F. Gould (Advances in Chemistry Series), No. 114, American Chemical Society, Washington, D.C., 1972.

[124] W. P. Purcell, G. E. Bass, and J. M. Clayton, 'Strategy of Drug Design', Wiley–Interscience, New York, 1973, Chaps. 5 and 6; P. N. Craig, ref. 123*b*, p. 115.

member in a class of drugs. Such studies are being made on several antileukaemic molecular types, such as, for illustration,[125] nitrosoureas (47), triazines (48), aziridines (49), and pyrimidines (50).



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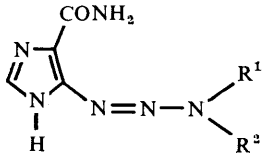

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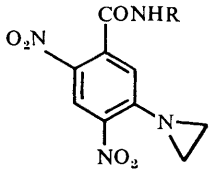
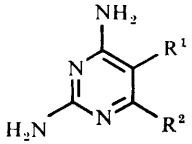


(49)



(50)

The Hansch treatment can give a partial answer to the questions of how many compounds in a given class should be tested and what is the probability that the most active member of a given class has been found. When applied to the nitrosoureas, for example, and neglecting steric and electronic effects, it predicts that for optimal therapeutic properties, the nitrosourea should have a log *P* value (*P* = partition coefficient between 1-octanol and water) in the range -1.5 to -0.5.[126] Higher log *P* values are associated with decreased antitumour activity or greater toxicity. Following this prediction, the cyclohexyl group in CCNU (11) was replaced by a carbohydrate moiety and the product was actually more active and less toxic than CCNU.[127] Perhaps this greater therapeutic value is due to the enhanced hydrophilic character of the compound or because the sugar serves as an effective carrier to the tumour cells. Antitumour activity is also correlated with a low carbamoylating activity.[128]

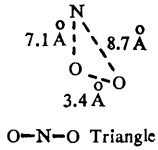
If tumour cells do have a large free-radical character, as implied earlier, then the use of radical substituent constants E_R[129] might give more significant and useful regression equations.

[125] C. Hansch, N. Smith, R. Engle, and H. Wood, jun., M. D. Anderson Symposium on Fundamental Cancer Research, Houston, Texas, February, 1974; E. J. Lein and G. L. Tong, *Cancer Chemotherapy Reports Part 1*, 1973, **57**(3), 251.
[126] J. A. Montgomery, J. G. Mayo, and C. Hansch, *J. Medicin. Chem.*, 1974, **17**, 477; A. N. Fujiwara, E. M. Acton, and D. W. Henry, *ibid.*, 1974, p. 392.
[127] J.-L. Montero, J. L. Imbach, and M. M. Mousseron, *Compt. rend.*, in press.
[128] G. P. Wheeler, B. J. Bowdon, J. A. Grimsley, and H. H. Lloyd, *Cancer Res.*, 1974, **34**, 194.
[129] T. Yamamoto and T. Otsu, *Chem. and Ind.*, 1967, 787.

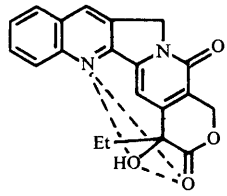
Although these Q.S.A.R. methods have a great potential, they provide little help in finding new molecular types with antitumour activity. The quantum chemical techniques provide a useful tool for learning more about drug–receptor site interactions, particularly conformations and charge distributions necessary for maximum interaction and molecular sites of reactivity.[130] Some of the molecular types exhibiting a range of antitumour activity have been reviewed recently.[131]

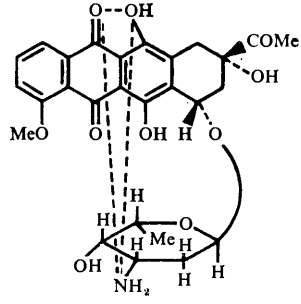
B. Target-specific Approach.—This method uses as a guide the structures of compounds known to localize in a certain part of the body or have a specific biological activity. Examples are metal chelates or organoboron compounds which concentrate in specific organs. For instance, CNS drugs with no known antitumour activity are molecularly altered to give them cytotoxic activity without destroying their ability to reach the brain or CNS. In one case, a group of phenothiazines among many psychotropic (tranquillizers, energizers) drugs were found to be active in the L-1210 tumour.

C. Active Molecular Fragment. It is the usual practice to seek a similar molecular fragment in a group of compounds exhibiting some property in common. An example among anticancer agents is the O—N—O triangulation observed in some non-alkylating antileukaemic drugs.[132] The presence of this molecular pattern does not mean that a compound must have antileukaemic activity but it is noteworthy that the O—N—O group can be found in several different classes of antitumour drugs including Adriamycin, MTX, and those shown below. It is hypothesized that such a structural fragment might assist the *in vivo* binding of the drug to one of the critical biological receptor sites involved in leukaemia genesis.



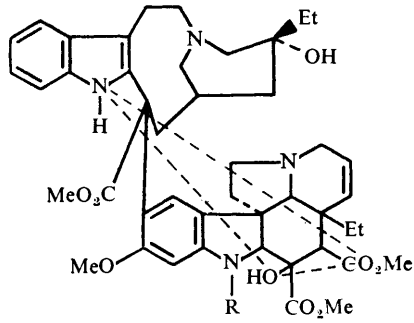
O—N—O Triangle



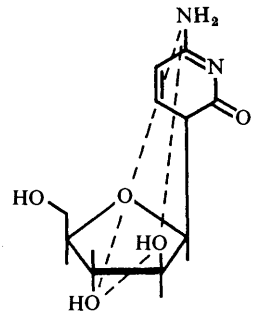


Daunomycin

[130] R. E. Christoffersen, D. Spangler, G. G. Hall, and G. M. Maggiora, *J. Amer. Chem. Soc.*, 1973, **95**, 8526.
[131] C. C. Cheng and K. Y. Zee-Cheng, *Ann. Reports Medicin. Chem.*, 1973, **8**, 128.
[132] C. G. Zubrod, *Life Sciences*, 1974, **14**(5), 809; K.-Y. Zee-Cheng and C. C. Cheng, *J. Pharm. Sci.*, 1970, **59**, 1630.



Vinblastine R = Me
Vincristine R = CHO



Cytosine arabinoside

D. DNA-intercalators.—Some drugs are known to form complexes with DNA and it is thought that antitumour activity is related to their intercalation between base pairs of the DNA chain.[133] Most of these agents are planar, polycyclic quinones or nitrogen heterocyclics with several methoxy- or hydroxy- groups attached. The binding characteristics of such compounds with DNA and other biological constituents are being studied by physical methods.

E. Multi-component Systems.—The rationale in this approach is to use an agent which is inert or non-toxic but which can be converted by enzymes or radiation into a cytotoxic substance at the tumour site. For example, masked alkylating agents have been used which are cleaved enzymatically or chemically to biological alkylating agents.[134] This same scheme is the foundation of the neutron capture technique.[135] Ideally, a drug containing an atom with a high rate of neutron capture would localize selectively in tumour cells. The irradiated drug would then emit destructive alpha particles to kill the nearby cells. Boron-10 and uranium-235 have large neutron capture cross-sections. Few non-toxic uranium compounds have been prepared but a number of boron-containing drugs have been found to concentrate preferentially in brain tumour cells. Although this technique offers promise of producing antitumour drugs, especially for brain cancers, no such compound has progressed beyond the clinical stage. Alternately, the B-10 could be incorporated into a tumour-specific antibody protein which would subsequently concentrate the boron in the tumour cell

[133] W. J. Pigram, W. Fuller, and L. D. Hamilton, *Nature New Biol.*, 1972, **235**, 17.
[134] K. C. Tsou, M. D. Anderson Symposium on Fundamental Cancer Research, Houston, Texas, February 1974; Z. B. Papanastassiou, R. J. Bruni, and E. White, V, *J. Medicin. Chem.*, 1967, **10**, 701.
[135] W. M. Baird, A. Dipple, P. L. Grover, P. Sims, and P. Brookes, *Cancer Res.*, 1973, **33**, 2386; A. H. Soloway, *Progr. Boron Chemistry*, ed. A. L. McCloskey and H. Steinberg, Pergamon Press, New York, 1964; A. H. Soloway, H. Hatanaka, and M. A. Davis, *J. Medicin. Chem.*, 1967, **10**, 714.

antigen. Neutron radiation could then be applied to kill specifically the tumour cells.[136]

Chemoimmunotherapy is yet another conceivable multicomponent system for cancer therapy. The basic concept consists of the preparation of tagged haptens which may be infused to label neoplastic cells. Then a cytotoxic antibody may be generated against these haptens.[137]

F. Natural Sources.—Not to be overlooked is the search for anticancer agents in agricultural and marine plants and animals. In this approach, the chase is guided by testing for antitumour activity, generally *in vitro* against KB cells. Promising fractions are then followed by *in vivo* tests against several animal tumours.[138] Such activity-directed isolation of new tumour inhibitors of plant origin has yielded several compounds which are in or nearing clinical trials, such as bruceantin (51), maytansine (19), ellipticine (45), taxol (52), and VM-26 (53).

5 Cancer Treatments Related to Chemotherapy

There are other modes of cancer treatment which are somewhat related to chemotherapy, such as radioisotope therapy and immunotherapy. In the former modality, a radioisotope is administered which is known to localize in an organ.[139] For example, iodine-131 is used for thyroid cancer, yttrium-90 coated microspheres for metastases in lung and liver cancer, or phosphorus-32 for lymphomas and leukaemias. Actually, a useful role that organic chemists can play here is to synthesize radiolabelled agents, not for radiation therapy but for diagnosing or locating tumours.[140] Thus, compounds known to accumulate selectively in certain tumours could be radio-tagged as a means of detecting the tumour. An example is stilbestrol di-iodide which localizes rapidly in prostate cancers. Other examples are 19-radio-iodinated cholesterol for the diagnosis of adreno-cortical carcinoma,[141] and radio-iodinated tyramines for adrenal medullary tumours.[142]

Immunotherapy is a promising mode of cancer treatment and warrants some comment here. In the 1890s, William Coley first injected 250 cancer patients with bacterial toxins who all improved and survived many years of life. However, his results were generally unaccepted for several decades.

Evidence of the role of the body's immunity system in fighting cancer comes in-

[136] M. F. Hawthorne, R. J. Wiersema, and M. Takasugi, *J. Medicin. Chem.*, 1972, **15**, 449; R. L. Sneath, jun., A. H. Soloway, A. S. Dey, W. D. Smolnycki, and S. M. O'Keefe, *J. Medicin. Chem.*, in press.

[137] A. H. Soloway, I. Agranat, A. R. Chase, R. E. Hernandez, E. S. Kimball, T. Cascieri, jun., and C. H. Cox, *J. Medicin. Chem.*, in press.

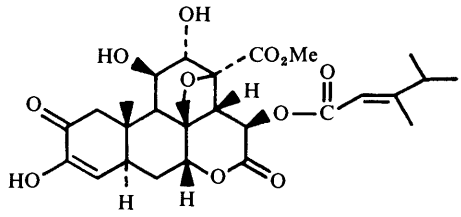
[138] S. M. Kupchan, *Fed. Proc.*, 1974, **88**(11), 2288.

[139] M. Brucer, in 'Progress in Clinical Cancer', Vol. 1, ed. I. M. Ariel, Grune and Stratton, New York, 1965, p. 74.

[140] R. E. Counsell and R. D. Ice, 'The Design of Organ Imaging Radiopharmaceuticals', University of Michigan, Ann Arbor, 1973; R. E. Counsell, T. Yu, V. V. Ranade, and A. Buswink, *J. Medicin. Chem.*, 1973, **16**, 1038, and previous articles.

[141] L. M. Lieberman, W. H. Beierwaltes, and J. W. Conn, *New Engl. J. Med.*, 1971, **285**, 1387.

[142] R. E. Counsell, T. D. Smith, V. V. Ranade, O. P. D. Noronha, P. Desai, T. Yu, and A. Buswink, *J. Medicin. Chem.*, 1973, **16**, 684, 1038.



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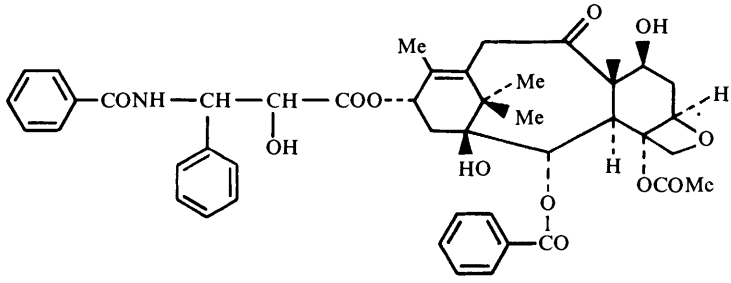

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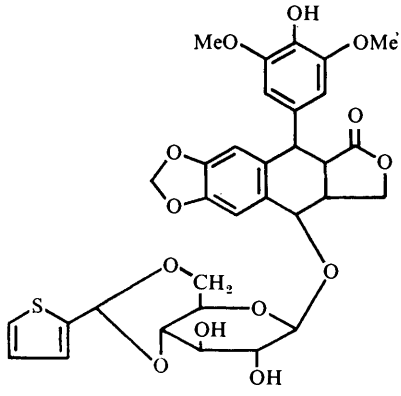


(53)

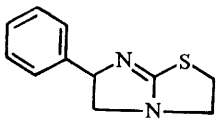
directly from several observations: (i) cancer strikes hardest in the young and the old, the two periods when the immune system is least organized; (ii) there is a high correlation between cancer and immuno-deficiency diseases, in which patients with a given type of tumour suffer from certain types of infections,

e.g. those with Hodgkin's disease, a cancer of the lymphoid system, are particularly susceptible to tuberculosis and viral infections, and those with multiple myelomas, cancer of the bone marrow, are vulnerable to streptococcus and pneumococcus bacterial infections, and (iii) cancer occurs 100-fold more frequently in transplant patients—patients whose immune systems are suppressed by drugs to prevent rejection of the new organ—than in the general population.

Our bodies make some 10^{11} cells (*ca.* 1 lb. of tissue) daily and it is statistically expected that some will be imperfect (estimates range from 10^4 to 10^6). Apparently, cells of neoplastic potential are continually being destroyed by our immune surveillance system, and the development of a tumour implies a breakdown in this process.

The immunological approaches used vary widely. Some doctors use Coley's bacterial-toxin formula; others inject vaccine made from killed mumps virus and diphtheria bacteria; many physicians prefer a live bacteria tuberculosis vaccine called *Bacillus Calmette–Guerin* (B.C.G.).[143] B.C.G., for instance, is used to stimulate the immune systems of patients suffering from malignant melanoma, a cancer that first appears on the skin and spreads rapidly to other parts of the body. Some of these patients have been free of the disease for two years or more. Administration of B.C.G. has also achieved remissions in patients with breast cancer and cancer of the thymus.

Candidates for B.C.G. immunotherapy are often chosen by a test of their immune sensitivity toward dinitrochlorobenzene—a reagent used to assess a patient's immune system.[144] Although some encouraging dramatic results have been achieved by immunotherapy, there are still many problems facing this modality of treating cancer patients.[145] One is the fact that most antitumour drugs suppress the immune system and another is the apparent presence of complexes in some cancer patients that prevent the immune system from attacking cancer cells. Because of the severe side effects usually occurring from B.C.G. treatment (fevers, liver disorders, inflammations and abscesses at the injection points), there is a wide international search for chemical stimulators of the immune system. Two promising compounds in extensive clinical trials are levamisole (54) and tilorone (55).[146]



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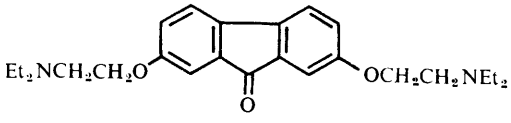

(55)

[143] P. H. O'Brien, *J. South Carolina Med. Assoc.*, 1972, **68**(12), 466.
[144] D. Morton, Report to the American Association for the Advancement of Science, San Francisco, Feb., 1974.
[145] R. T. Prehn, Proceedings of the 10th Canadian Cancer Research Conference, 1973, ed. P. G. Scholefield, University of Toronto Press, Toronto, 1974, p. 136.
[146] H. J. Sanders, *Chem. and Eng. News*, Dec. 23, 1974, p. 14.

Whereas the major thrust of cancer chemotherapy is the destruction of malignant cells after they have been formed, immunotherapy is aimed at the preneoplasia phase—the period between exposure to carcinogen or initiation and the transformation to malignancy. This induction or preneoplasia period may last 20 or more years. Another effort to halt oncogenesis at the preneoplasia point is being made by the administration of vitamin A or its analogues. Some of the evidence of the role of vitamin A or its congeners was presented at a conference at the National Institutes of Health, Washington, November, 1974, sponsored by the N.C.I. and Hoffmann–LaRoche.[147] It was shown, for example, that various carcinogens bind much more tightly to DNA in cultural hamster tracheas from vitamin A-deficient hamsters than to DNA in tracheas from healthy animals. Also, colon tumours produced by aflatoxin B_1 are more prevalent in rats deficient in vitamin A than in normal controls. Others showed that vitamin A exerts a protective action when fed to animals simultaneously with known carcinogens. It is noteworthy that there is a higher incidence of lung cancer among persons with vitamin A deficiency.[18]

As with other types of medication, tumours change their sensitivities toward a given drug. Hence there is a biochemical problem to learn the mechanisms of anticancer drug resistance. In the case of alkylating agents, for instance, it is possible that deactivation results from reaction of the drugs with non-protein sulphydryl groups.[148] Any number of modes of deactivation are conceivable, *e.g.*[149] decreased concentration of critical targets or masking of the active functional groups, changed cellular transport, increased competition by normal or protective metabolites for an enzyme, the drug, or for an essential metal ion, failure of the necessary activation of the drug, to name a few.

6 Conclusion

The major criterion used to measure the success of the chemotherapy programme is the number of patients to achieve normal life expectancy who would otherwise have died from cancer. There are now ten human cancers which are highly responsive to chemotherapy and 50 per cent of these patients should achieve normal life expectancy.[150] Although longer remissions of many cancers are achieved through chemotherapy, these successes do not include the big cancer killers such as breast, colon, or lung cancer so that the incidence of cancers is still on the rise.

Drugs now in use are not highly effective against old tumours which have low rates of DNA synthesis, such as colon and lung cancer: *e.g.*, the median survival rate of all lung cancer patients from diagnosis to death remains less than six months.[151] To make the big breakthrough here, we will need a better understanding of the mechanisms of action of antitumour agents. The identi-

[147] *Cf.* T. H. Maugh, jun., *Science*, 1974, **186**, 1198.
[148] G. P. Wheeler, *Cancer Res.*, 1963, **23**, 1334.
[149] Symposium, *Cancer Res.*, 1965, **25**, 1581.
[150] C. G. Zubrod, *Cancer*, 1972, **30**, 1474.
[151] O. S. Selawry, *Cancer Chemotherapy Reports Part 3*, 1973, **4**(2), **5**.

fication of additional biochemical targets for antitumour agents would help too. Known targets of some clinically established drugs are:[152]

Drug	*Target*
Methotrexate	Dihydrofolate reductase
5-Fluorouracil	Thymidylate synthetase
Hydroxyurea	Ribonucleotide reductase
Arabinosylcytosine	DNA Polymerase
Actinomycin D and Adriamycin	Intercalation with DNA
Nitrogen mustard and CCNU	Reaction with DNA
6-Thioguanine	Incorporation into DNA
Vincristine	Mitotic blockade

Hence, biochemical mechanistic studies of carcinogenesis and cytotoxic actions are sorely needed. It is generally believed that the rational design of cancer drugs will ultimately be based on an exploitable biochemical difference between normal host cells and the invading cancer cells.

Moreover, in all previous successes over biological systems with chemicals, *e.g.*, antimalarials, pesticides, *etc.*, the development of cellular resistance has always necessitated a change in the bioactive chemicals used. Consequently, eventually resistance to the present successful cancer drugs can be expected and our search for new drugs must continue unabated.

Two recent strategies for more effective use of our present arsenal of drugs are described below:

(i) to administer several drugs either together or in succession;[153] only a few drugs effect cures when used singly, such as CTX for Burkett's tumour, MTX in choriocarcinoma, or Actinomycin D in Wilm's tumour. Drugs for combination are usually chosen on a basis of having different modes or sites of action, different times of action in the cell cycle,[154] or different host resistances or carcinostatic action.[155] One variation here is the 'rescue' technique of administering an excessive quantity of a drug, a potentially lethal amount, and shortly thereafter of giving the patient an antidote to counteract the action of the antitumour drug.[156] (ii) A second modification in the practice of chemotherapy is an early combination of chemotherapy with surgery and/or radiation therapy.[157] An excellent example of this is the recent finding that the administration of

[152] J. A. R. Mead, M. D. Anderson Symposium on Fundamental Cancer Research, Houston, Texas, February, 1974.

[153] J. R. Bertino, M. B. Mosher, and R. C. DeConti, *Cancer*, 1973, **31**, 1141; H. H. Hansen, *Cancer Chemotherapy Reports Part 3*, 1973, **4**(2), 25; A. Goldin, *ibid*, p. 189.

[154] V. H. Bono, jun., *Cancer Chemotherapy Reports, Part 2*, 1974, **4**(1), 131; A. M. Zimmerman, G. M. Padilla, and I. L. Cameron, 'Drugs and the Cell Cycle', Academic Press, New York, 1973.

[155] W. M. Kirsch, D. Schulz, J. J. Van Buskirk, and H. E. Young, *J. Med. (Basel)*, 1974, **5**, 69.

[156] M. Levitt, M. B. Mosher, R. C. DeConti, L. R. Farber, R. T. Skeel, J. C. Marsh, M. S. Mitchell, R. J. Papac, E. D. Thomas, and J. R. Bertino, *Cancer Res.*, 1973, **33**, 1729; Staff report, *Chem. and Eng. News*, April 8, 1974, p. 21.

[157] S. K. Carter, *Cancer Chemotherapy Reports Part 2*, 1974, **4**(1), 3; F. O. Stephens, *Med. J. Austral.*, 1972, **1**(12), 591.

L-PAM (10) immediately following a simple mastectomy for breast cancer is more effective than a radical mastectomy. In the past, drugs have usually been given when cancers had reached the inoperable stage, when chemotherapy has a lower probability for success.

There are four widely used modes of cancer treatment: surgery, radiation therapy, chemotherapy, and immunotherapy. There are other less developed approaches being explored, such as electrosurgery, chemosurgery (use of zinc chloride paste *in situ*) cryosurgery (use of liquid nitrogen),[158] and thermotherapy.[159] In the latter modality, either local or total-body hyperthermia (excess heat) is used to destroy cancer cells and potentiate the immune response. It appears that tumour growth increases at temperatures above 37.5 °C until about 42 °C where there is a sudden inhibition of metabolism.

This review was devoted to the more chemical aspects of cancer but there are other major phases which inter-relate with the chemotherapy programme: *e.g.*, studies are being made to find better screening methods[160] and develop screens using transplanted human cancer cells.[161] Clinical and preclinical testing of drugs is a big operation, involving extensive biostatistics;[162] the pharmacological and toxicological actions of drugs must be learned prior to making clinical trials, and the logistics of drug acquisitions must be well organized. Also, important supportive studies are being made in an attempt to understand DNA replication, control of gene expression in animal and human tissue, and the interaction of known effective antitumour agents with these processes.[163] The epidemiology of cancer is an international co-operative programme,[164] and the recognition and removal of environmental carcinogens will undoubtedly be a major factor in the success over cancer. Rather than the prevention of cancer, it may turn out that the best that can be hoped for in cancer treatment is its control.[165] Probably the greatest long-range chances of conquering cancer lie in the success of immunotherapy and the elimination or avoidance of environmental carcinogens.

We see then, that there are many ways in which chemists can help in the war on cancer. This includes analytical, inorganic, organic, pharmaceutical, and physical chemists, and, of course, biochemists.

The author is grateful to the National Cancer Institute for making assessable much of the information given herein, particularly that from outside the U.S.

[158] W. A. Clabaugh, *Amer. Fam. Physician*, 1973, 7(5), 78.
[159] J. A. Dickson, *Cancer Chemotherapy Reports Part 2*, 1974, **58**, 294; D. S. Muckle, *Cancer Therapy Abstracts*, 1974, 3(15), No. 74-1045, 214.
[160] F. E. Knock, R. M. Galt, Y. T. Oester, and R. Sylvester, *Oncology*, in press; F. E. Knock, R. M. Galt, Y. T. Oester, and R. Sylvester, *S. African J. Med. Sci.*, 1973, **38**, 43.
[161] L. M. Cobb and B. C. V. Mitchley, *Cancer Chemotherapy Reports Part 1*, 1974, **58**(5), 645.
[162] M. Zelen, *Cancer Chemotherapy Reports Part 3*, 1973, **4**(2), 31.
[163] F. M. Thompson, A. N. Tischler, J. Adams, and M. Calvin, *Proc. Nat. Acad. Sci. U.S.A.*, 1974, **71**, 107.
[164] International Agency for Research on Cancer, *Science*, 1972, **178**, 844.
[165] 'Chemotherapy of Cancer Dissemination and Metastasis', ed. S. Garattini and G. Franchi, Raven Press, New York, 1973.

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