The title that was assigned to me is a clear invitation to pontificate. Instead, I will share with you a few modest and not very original thoughts and speculations. These are based on a large literature and a small experience of tilling the soil among certain obscure and unnatural pyrimidines. This engagement with the rationality of antimetabolites followed an ignoble exodus from the quagmire surrounding an even more obscure alkylating agent. Thus, my bias is already exposed.

It is not my purpose to cover the enormous literature in these two fields of alkylating agents and antimetabolites. Rather, I shall refer to reviews whenever possible. Nor do I intend to explore systematically structure-activity relationships of every series of compounds, detailed screening results, comparative toxicology, clinical pharmacology, and mechanisms of action. I will try merely to focus on certain facts, trends, and promising leads that happen to interest me and suggest points of departure for future synthetic chemical forays. I shall emphasize drug design at the expense of ignoring the exciting advances in cell-cycle kinetics and clinical combination chemotherapy that have been emphasized elsewhere in this Symposium. I shall forbear from intoning the customary litany of our ignorance of the essential molecular lesions of malignancy and intend to proceed with what is known. But I had better proceed.

ALKYLATING AGENTS

The alkylating agents as a group are among the clinically most useful compounds in cancer chemotherapy. Their chemistry and attempts to design agents showing selectivity of action have been reviewed by Ross (46). Hirschberg (24) has made a very comprehensive compilation of the earlier information about their chemotherapeutic properties, and this has been expanded and brought up to date by Ochoa and Hirschberg (39). Various aspects of the mechanism of action of alkylating agents in many systems have been reviewed by Brookes and Lawley (7), Lawley (32), Wheeler (57, 58), and Warwick (56). Oliverio and Zubrod (40) have discussed their clinical pharmacology.

The alkylating agents with chemotherapeutic activity are chemically reactive and at least difunctional. The structures of a few of the important compounds are shown in Chart 1. Compound I is sulfur mustard, the original prototype, and II–VIII are members of the nitrogen mustard (HN2) family, with their characteristic β-chloroethyl groups. Two examples of ethylenimines (aziridines) are IX and X, and the remaining important class of methane sulfonates is illustrated by Myleran (XI). Literally thousands of these compounds have been synthesized, in which the reactive β-chloroethyl, ethylenimine, or methane sulfonate groups have been hung onto innumerable “carriers,” which some mystics endow with remarkable biologic specificity. Thus, we have phenylalanine mustard (V, Sarcolysin, Melphalan), uracil mustard; VII, cyclophosphamide (Cytoxan, Endoxan); VIII, 1,3-bis(2-chloroethyl)-1-nitrosourea, BCNU; IX, triethylenemelamine (TEM); X, Thio-TEPA; XI, Myleran.

![Chart 1. I, sulfur mustard; II, nor-HN2; III, nitrogen mustard, HN2; IV, Nitromin; V, phenylalanine mustard (Sarcolysin, Melphalan); VI, uracil mustard; VII, cyclophosphamide (Cytoxan, Endoxan); VIII, 1,3-bis(2-chloroethyl)-1-nitrosourea, BCNU; IX, triethylenemelamine (TEM); X, Thio-TEPA; XI, Myleran.](image-url)
these data have been provided by a truly heroic and monumental study by Schmidt et al. (50). These investigators studied 51 β-chloroethylamines, 25 aziridines, 39 methane sulfonates, and 12 nonalkylating compounds for their toxicity to mice, rats, dogs, and monkeys and their activities against 18 transplanted rat tumors and 7 transplanted mouse tumors. This tour de force was published in a monograph of 1528 pages (50).

It has been alleged by many that the proof of the chemotherapeutic specificity of the "carrier" rests on the "fact" that the L-phenylalanine mustard has greater tumor-inhibitory effectiveness than the D isomer or the DL mixture (V). Let us examine the most reliable information on this subject as presented by Schmidt et al. (50). Their data on the rat tumors are given in Table 1. At the bottom of the table is the mean for 10 tumors of the ratio of the LD10/ED90 (or ED40), the therapeutic index, for the L isomer over the D isomer, which is 1.05 ± 0.19. Thus, there is no difference in the therapeutic index of the two isomers although, admittedly, the L isomer is more toxic and is more active against the tumors than the D isomer. On the other hand, when the ratio of the L isomer to the DL mixture is taken for 16 tumors, it is 0.76 ± 0.08. This finding that the DL mixture has a better therapeutic index than the L isomer resists rational explanation. However, the same comparison in mouse tumors represents the proof for the chemotherapeutic specificity of the "carrier," then the case is lost, even though there are differences in overall toxicity. Schmidt et al. (50) have concluded that "with possibly two exceptions, both in the methane sulfonate series, there was no indication that specific classes of alkylating agents or members within a class were endowed with unique antitumor activity. Apart from these exceptions, cyclophosphamide (VII) and the isomeric phenylalanine mustards (V) were the outstanding representatives in virtually every test system examined whether the neoplasm was highly sensitive or relatively insensitive to alkylating agents."

Let us now examine cyclophosphamide (VII, Cytoxan, Endoxan) a little more closely. This compound "was designed in accordance with the principle of transversion of an inactive transport form to an active form at special sites in the body" (5). It was thought that tumors are rich in phosphoamidases, and hence that the P-N bond would be selectively cleaved in the tumor to activate the drug. However, it was soon found that cyclophosphamide was not active against the growth of tumor cells in culture but was metabolized to an active form in the liver (15). Hence, the properties of the compound were as designed, except that the activation takes place in the liver rather than in the tumor. Since that time a great deal of work has been done, particularly by Brock (5) and Friedman (17) to elucidate the nature of this activation process. It was originally believed that after a series of hydrolyses, nor-HN2 (II) was liberated and was the therapeutically active compound. However, this does not seem to be so, and the present state of this exceptionally complicated situation appears to be that the metabolism of cyclophosphamide in vivo does not parallel its chemical behavior. Considerably more work is needed before an understanding is reached of the almost unique tumor-inhibitory activity of cyclophosphamide.

Another compound of particular interest is 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (VIII), which is unusual in that it crosses the blood-brain barrier and is active against intracerebral L1210 leukemia (49). Although it contains β-chloroethyl groups, there is some doubt as to whether it is really an alkylating agent, since it reacts to only a slight extent with 4(μ-nitrobenzyl)-pyridine (59). It inhibits DNA and RNA synthesis in L1210 leukemia cells in vivo and in vitro (60), and its effect on a DNA polymerase system is comparable to that of β-chloroethylisocyanate; it appears to react with the enzyme rather than with the primer (61).

It is clear that there is very little relationship between the distribution, excretion, and metabolism of the alkylating agents and their mechanism of action (39, 40). Although they are often considered to be "radionimetic" compounds, this

<table>
<thead>
<tr>
<th>Tumor</th>
<th>L</th>
<th>DL</th>
<th>L/D</th>
<th>D</th>
<th>L/D</th>
</tr>
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<tr>
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<td>15</td>
<td>1.13</td>
<td>10</td>
<td>1.70</td>
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<td>1.00</td>
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<tr>
<td>Walker 256, CH, ascites</td>
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<td>31</td>
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<td>44</td>
<td>0.45</td>
<td>14</td>
<td>1.42</td>
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<td>54</td>
<td>0.61</td>
<td>15</td>
<td>2.20</td>
</tr>
<tr>
<td>Dunning IRC-741 leukemia, subcutaneous</td>
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<td>2</td>
<td>1.00</td>
<td>3</td>
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<tr>
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<td>5.5</td>
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<tr>
<td>Lymphoma 8, subcutaneous</td>
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<td>1</td>
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<td>1</td>
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<tr>
<td>Adenocarcinoma R-35, subcutaneous</td>
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<td>4</td>
<td>0.62</td>
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<tr>
<td>Adenocarcinoma R-35, pulmonary</td>
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<td>2.5</td>
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<td>Murphy-Sturm lymphosarcoma, subcutaneous</td>
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<td>1</td>
<td>1.00</td>
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<td>5.5</td>
<td>0.46</td>
<td>2.5</td>
<td>0.46</td>
</tr>
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</table>

Effects of optical isomers of phenylalanine mustard on transplantable rat tumors (50). LD10/ED90 or LD10/ED60.

- L/D: mean of 16 tumors, 0.76 ± 0.08.
- bL/D: mean of 10 tumors, 1.05 ± 0.19.
analogy is probably overdone (56). Studies on the mechanism of resistance of experimental tumors to alkylating agents have been critically reviewed by Wheeler (58). The main fact is that there is considerable cross-resistance among these structurally diverse compounds, but Wheeler (58) cautions against assuming from that fact that the alkylating agents act by a common mechanism; he considered altered permeability as an important factor in resistance, and the repair of alkylated DNA (see below) was unknown at that time.

What then is the mechanism of action of the alkylating agents, if, indeed, a single mechanism exists? It appears from an overwhelming body of data that the primary action of these compounds is a direct attack on DNA. The chemistry of this has been worked out in a brilliant series of investigations by Brookes and Lawley, which has been reviewed by Lawley (32).

They showed that sulfur mustard (I) exerts a nucleophilic attack on the N-7 of guanine residues in the DNA, which labilizes the glycosidic bond and causes the release of guanine from the DNA, which can thus give rise to mutations. They also showed that sulfur mustard could react with two guanines to produce a cross-linking, which they postulate to be the primary cytotoxic action, and which would prevent DNA replication (7). They have demonstrated with sensitive and resistant strains of bacteria that in the latter there is an active repair mechanism that excises the cross-linked guanines from the DNA (33). They also found in bacteria that similar cross-linking was obtained with triethylenemelamine (TEM) (IX) and butadiene diepoxide, and produced additional evidence that the cross-linking is interstrand (34). Crathorn and Roberts extended this work to mammalian cells (HeLa) and have demonstrated that with sulfur mustard there is a direct relationship between lethality and attack on DNA; they also found repair-excision of alkylated guanines from the DNA (11). Ruddon has reported that DNA reacted with HN2 (III) has a decreased template activity for RNA polymerase, and to a lesser extent for DNA polymerase (48), which is opposite to the inhibitory effects of nucleic acid biosynthesis found in intact cells.

However, the view that the primary chemotherapeutic effect of alkylating agents results from their attack on DNA is not universally accepted, largely upon the basis of work done in mice with tumors. Golder et al. (19) found that the extent of alkylation by HN2 was very slight and that there was some evidence of crosslinking DNA to protein. Wheeler and Alexander (59) studied the in vivo alkylation of sensitive and resistant tumors implanted bilaterally into the same mouse, and found no correlation between the extent of alkylation of the DNA and chemotherapeutic effect. However, it is evident to all those who are concerned with the binding of carcinogens to DNA that there is considerable specificity in binding, and in fact Doskocii and Sormova (13) have found that not all guanines in DNA are equally reactive to sulfur mustard. Until the nature of this specificity is understood, the mechanism of action of the alkylating agents will remain somewhat obscure.

What then is the need for additional alkylating agents? Schmidt et al. (50) have stated, “In one sense the lack of specificity of the various alkylating agents in both the therapeutic activity and toxicity spheres is disappointing. On the surface at least, it offers little hope that any agent of this chemical type will be found which will affect some neoplasms in a unique way . . . .” Therefore, I feel that continuation of a vast effort of synthesis aimed at the random attachment of alkylating groups to a fanciful collection of “carriers” can no longer be justified. However, there appear to me to be three areas in which specific and rational syntheses could be justified at this time: (a) preparation of possible metabolites of cyclophosphamide and its derivatives, (b) synthesis of further derivatives of BCNU, and (c) once we have a much more sophisticated knowledge of the parameters regulating the specificity of the attack on DNA, this information might be put to use in the area of drug design.

ANTIMETABOLITES

Let us herewith define a metabolite as some naturally occurring compound produced during metabolism and an antimetabolite as a compound related structurally to the metabolite which prevents its further utilization by competing with it for an enzyme. This definition and field came out of the pioneering efforts of D. D. Woods (64), who in 1940 recognized the metabolite-antimetabolite relationship of p-aminobenzoic acid and sulfanilamide. The role of these compounds in pharmacology and biochemistry was explained when the structure and function of folic acid were elucidated. Reviews of various aspects of cancer chemotherapy with antimetabolites of many sorts have been provided by Stock (53), Langen (30), Baker (2), and Timmis (54).

Antifolies

The antifolies in cancer chemotherapy have three distinctions: (a) they were the first compounds to be effective against acute leukemia in children; (b) they cure a high percentage of female patients with choriocarcinoma; and (c) they are now where the action is.

Folic acid (XII) is reduced to tetrahydrofolate by the enzyme dihydrofolate reductase, which is powerfully inhibited by antifolates such as Amethopterin (XIII, Methotrexate). Tetrahydrofolate reacts with formaldehyde (or other compounds at the same oxidation level) to give isomeric formyl or methylene tetrahydrofolates, which are the coenzymes of all one-carbon metabolism. Consequently, these coenzymes are required for two steps of purine synthesis and for thymidylate synthetase. A great deal of work has been done on the mechanism of resistance to antifolies, and suffice it to say that this is not fully understood at present. Although Amethopterin is a very powerful inhibitor of dihydrofolate reductase, there is still a need to obtain more selective and specific compounds.

A simple modification, by the addition of a methylene group to give homofolic acid (XIV), has been studied by Friedkin et al. (43). They have found some antimalarial activity with this compound and have further demonstrated that tetrahydrohomofolates are inhibitors of thymidylate synthetase. Very recently, Hutchison (27) has reported that a series of quinazoline analogs, of which XV is the most active, exert greater inhibitions of bacteria and tumor cell growth than does Amethopterin. Obviously, further work along these two lines is indicated.
A classical study of dihydrofolate reductase inhibition by another series of inhibitors, the 2,4-diaminopyrimidines, illustrated by XVI, Daraprim, an active antimalarial, has been carried out by Hitchings (25). He has studied the kinetics of interaction of a series of these compounds with dihydrofolate reductases isolated from bacteria and various protozoa and has found striking differences. This makes it possible to achieve a remarkable specificity in the chemotherapy of infectious disease by taking advantage of these species differences in enzymes.

Baker has for many years been working on "active-site-directed irreversible inhibitors" of various enzymes, including dihydrofolate reductase. This productive research has been described in his book (2) and in innumerable papers since. By studying the kinetics and nature of the inhibition of this enzyme with a large number of structurally related compounds, he has "mapped" the region of the active site in terms of ionic and hydrophobic regions. As the near-culmination of this approach, Baker and Meyer (3) have recently reported that compound XVII has the fantastic specificity of being a powerful irreversible inhibitor of the enzyme isolated from LI210 cells, but not from mouse liver, spleen, and intestine! This finding has remarkable connotations as to the nature of the carcinogenic change, but it cannot yet be interpreted. Surely, this compound must be the "magic bullet" that we have all been searching for, with apparent specificity for irreversible inhibition of only the tumor enzyme. Unfortunately, however, this compound is inactive in vitro at inhibiting the growth of LI210 cells which are presumably impermeable to the compound (3). Hopefully, this difficulty may not be insurmountable. If so, we can look forward to inhibitors of dihydrofolate reductase with unsurpassed specificity to cancer tissue. Here, then, is a supreme example of carrying out enzymatic structure activity studies combined with skillful and imaginative chemistry.

These latter studies of Hitchings (25) and Baker (3) gave rise to the third category of distinction listed above.
Additional Alkylating Agents and Antimetabolites

studied, is biologically active and is incorporated into DNA (36). It has also been found that 6-methylmercaptopurine ribonucleoside has quite a different mechanism of action than 6-mercaptopurine (6-MP) and its ribonucleoside (4), and that the periodate oxidation product of its ribonucleoside inhibits tumor growth and has other interesting biologic actions (28).

Another interesting compound is 4(5)-(3,3-dimethyl-triazene)-imidazole-5(4)-carboxamide (XXIII), which is an analog of an intermediate in purine biosynthesis and has considerable clinical activity against melanomas (51). Its biochemical mode of action is not yet known (to this author), but it represents an important new series of compounds that is worthy of further chemical and biochemical exploration.

Arabinosyladenine (XXV) has considerable activity against some tumors, and studies of its mechanism of action have been carried out (cf. 10, 23). Several purine nucleoside antibiotics with interesting structures and tumor-inhibiting activity have been isolated, characterized, and studied. These include Cordycepin (XXVI), Psicofuranine (XXIV), Tubercidin, Toyo-camycin, Sangivamycin (XXVII), and Formycin (XXVIII) (cf. 16). This latter compound is of particular interest because a number of its biologic properties have been explained by Ward and Reich (55) as being due to the fact that, in polynucleotide form, its individual residues exist in the syn, rather than in the common anti, conformation. This poses interesting possibilities for other C-nucleosides.

Isopentenyl adenosine (XXIX) was isolated from transfer RNA and its structure determined by Hall et al. (20). It was found to be a powerful cytokinin in plants and also had inhibitory activity against tumor cells and possibly against acute leukemia in children. Because of this interesting activity, a number of related compounds have been synthesized and tested by Fleysher et al. (14).

Although this presentation has been necessarily brief and superficial, it is clear that there are a number of interesting structural modifications of purine nucleosides with biologic activity. There are also several other different types of structural modifications that I have not listed here. Therefore, it is quite clear that further synthetic work with purine and purine nucleoside analogs should be biologically, and probably chemotherapeutically, rewarding.

Pyrimidine Antimetabolites

Some general reviews of this subject are those of Stock (53), Langen (30), Baker (2), Timmis (54), and Brockman (6).

The pyrimidine bases that occur in the nucleic acids are uracil (XXX), thymine (XXXI), and cytosine (XXXII). The only pyrimidine antimetabolite that is chemotherapeutically active as the free base is 5-fluorouracil (FU) (XXXIII), which was originally synthesized on the basis of a very definite rationale. With all other pyrimidine analogs, the nucleosides are required for biologic activity. A derivative more active than FU is 5-fluoro-2'-deoxyuridine (FUDR) (XXXIV); and trifluorothymidine (XXXV), in addition to being a potent tumor inhibitor, is also the most active compound known to inhibit the replication of DNA viruses. These compounds have been thoroughly reviewed (22, 23). 5-Iodo-2'-deoxycytidine (IUDR), (XXXVI) is clinically active against herpes simplex keratitis and is incorporated into DNA instead of thymine, but it has been disappointing in cancer chemotherapy (cf. 23). An interesting approach to increasing the chemotherapeutic effect of a close relative, 5-ido-2'-deoxycytidine (ICDR), was made by Woodman (63), who complexed the 5'-phosphate of ICDR with various polycations and found that it was incorporated into mouse tumor DNA in vivo to a considerably greater extent than was the nucleoside. Such an approach may find application to other nucleotide analogs.

Arabinosylcytosine (ara-C) (XXXVII) is a compound that is very active against tumors, human acute leukemias, and DNA viruses (cf. 10, 23). Its mechanism of action is also under intensive study. It is rapidly deactivated by deamination to arabinosyluracil (ara-U), and interesting research has been carried out to find inhibitors of this deaminase in the hope of increasing the chemotherapeutic effects of ara-C (8).

Isosteric replacements have also been fruitful with pyrimidine nucleosides. 6-Azauridine (XXXVIII) and 5-azauridine (XXXIX) have shown moderate activity against various tumors, and this field has been reviewed by Skoda (52). It is of interest that although trifluorothymidine and 6-azathymidine
Charles Heidelberger

have biologic activity, a compound, 5-trifluoromethyl-6-aza-2'-deoxyuridine, that combines both substitutions, was biologically inert (12). Another compound with an isosteric replacement that has activity against bacteria and tumor cells in culture is 3-deazacytidine (XL) as very recently reported by Robins et al. (45). In our laboratory we are synthesizing comparable compounds in the deoxyribonucleoside series, as well as other pyrimidine nucleoside analogs with isosteric replacements. Langen and Kowollik (31) have recently prepared 5'-fluorothymidine (XLI), which is active against thymidylate kinase, and hence is a nucleotide, rather than a nucleoside, analog.

A compound that appears superficially to resemble a pyrimidine nucleoside in the antibiotic Showdomycin (XLII) (cf. 16). However, biochemical work by Roy-Burman et al. (47) indicates that it does not act as a pyrimidine analog, but rather it inhibits various enzymes as a consequence of the alkylation properties of the maleimide moiety.

As in the case of the purine antimetabolites, the pyrimidine nucleosides are continuing to provide interesting new pharmacologically active compounds, including many that are not specifically mentioned here. Further chemical efforts in this field seem to be fully justified.

Polynucleotides

There is now abundant evidence that mammalian cells can take up intact polynucleotides. This has been reviewed for DNA by Ledoux (35), and Glick has shown that DNA obtained from mouse thymus can actually inhibit the growth of L1210 tumors in vivo (18). In our own studies, we made oligonucleotides of FUDR-5'-phosphate (FUDRP) in 1961 (44), but these did not show any greater activity than FUDR at inhibiting the incorporation of formate into the DNA thymine of Ehrlich ascites cells in vitro.

An important recent discovery by Park and Baron (41) demonstrated that double-stranded poly-inosinic:polycytidylic acid preparation (poly-IC) is capable of preventing or inhibiting viral replication in vitro and in vivo by stimulating interferon production. Very recently, Levy et al. (37) and Homan et al. (26) have reported that poly-IC inhibits the growth of several tumors in mice, and they have done some pharmacologic studies with the polymer. This opens up an exciting new field of macromolecular chemotherapy. Particularly when more is known about the mechanisms of these effects, it appears possible that major advances in specific cancer chemotherapy may be in the offing. In these days of wild speculations about genetic engineering, it may not be totally inappropriate to prophesy that one day cancer may be reversed by appropriate polynucleotide chemistry [for a review of the chemistry of polynucleotides, see Michelson et al. (38)]. For example, if as proposed by Pitot and Heidelberger (42), carcinogenesis is the result of the perpetuated deletion of a repressor, then if the messenger RNA that codes for this repressor were synthesized, it could cause the revision of that cancer to normal. Impossible? Who knows?

Other Miscellaneous Antimetabolites

Again, the listing of these compounds will not be complete, but are selected arbitrarily according to my current interests. Glutamine (XLIII) is an important biosynthetic intermediate, and diazo-oxo-norleucine (DON, XLIV) is its antimetabolite. In view of the interesting therapeutic effects of L-asparaginase, Handschumacher et al. (21) designed an analogous inhibitor of the substrate asparagine (XLV), namely diazo-oxo-nor-L-valine (XLVI), which they showed to have enzymatic specificity. Such an approach may be applied to other amino acids, should other enzymes of amino acid metabolism be found with tumor-inhibitory activities.

Hydroxyurea (XLVII) has been shown at high concentrations to be a reversible inhibitor of DNA synthesis (65), and it has some cancer chemotherapeutic activity which has stimulated the synthesis of related analogs. It has been shown by Krakoff et al. (29) to be an inhibitor of ribonucleoside diphosphate reductase.

Lastly, I would like to consider three aldehydes. Very recently Apple and Greenberg (1) reported that the combination of two metabolites in minor branches of the 3-carbon stage of glycolysis, 2-oxopropanal (XLVIII) and 2,3-dihydroxypropanal (XLIX), cured some mice with transplanted tumors. It has been demonstrated by Ciarami et al. (9) that L-erythro-2,3-dihydroxybutyraldehyde, an inhibitor of protein synthesis and not of glycolysis, has considerable antitumor activity. Thus, it appears that more synthesis of aldehydes may be in order.

CONCLUSIONS

What is the need for additional alkylating agents and antimetabolites? In my opinion there is no need for additional alkylating agents dreamed up ad hoc, but possibly there is a need for compounds specifically designed relative to the
interest in the metabolism and modes of action of cyclophosphamide and BCNU. I hope that I have made a convincing case for the need for the design and preparation of additional antimitabolites. The limits for these should only be the imagination and vision of the investigator and his chemical skill.

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The Need for Additional Alkylating Agents and Antimetabolites

Charles Heidelberger


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