PHR *Review*

The Chemical Control of Cancer

By JAMES F. HOLLAND, M.D.

SATISFACTORY THERAPY for most patients with cancer has not been achieved. The advances in surgery which permit more extensive operations and the increased control of tumors which can be exerted by the newer techniques and more powerful equipment of modern radiotherapy still fall desperately short of solving the problem. Most physicians are legitimately skeptical that further advances in these two disciplines can successfully cope with the challenge.

In 1953 approximately 224,000 people died from cancer in the United States (*1*). Of all patients with malignant disease, it is probable that only one-fourth to one-third are cured today. Full use of present knowledge and better methods for earlier diagnosis would surely save more lives. There remain, however, millions of persons who will die from cancer in the foreseeable future despite the most informed use of surgical or radiotherapeutic procedures, and regardless of the most meticulous attention to diagnostic techniques.

If an understanding of life is ever achieved in biochemical terms, it is a fair assumption that insight into the mechanisms of cancer will be realized pari passu. Despite the present lack of this understanding, two investigative approaches could be extended with reasonable hope of finding useful clinical applications.

The first approach, studies of carcinogenesis, may elucidate avoidable environmental or endogenous factors which, though now unknown, may be responsible for many cancer deaths. Recognition and avoidance of certain carcinogenic materials in the environment in the past have diminished their hazard. The observations of Pott in 1775 on carcinoma of scrotal skin in chimney sweeps (*2*) antedated by decades the appreciation of potential carcinogenicity associated with beta-naphthylamine and benzidine (bladder), ultraviolet radiation (skin), X-irradiation (skin, marrow, bone), and arsenic (skin), to name but a few well-established examples. Many other substances have been suspected of significant roles in human carcinogenesis: cigarette smoking (lung), urban soots (lung), chromate (lung), asbestos (lung), and smegma (penis and cervix) (*3–6*).

The positive identification of carcinogens is difficult. This difficulty may better be appreciated if it is recalled that the identity of the cancerous process in all its different types and loci is far from certain; there may be as many endogenous carcinogens as there are cancers, and perhaps multiple conditions must be satisfied for malignant growth to occur (*7, 8*). Despite the enormity of the task, the possibility is real that etiological and pathogenic factors can be identified and can then be avoided or counteracted. Research in carcinogenesis is deserving of the most intensive studies.

Chemotherapy of cancer is the second ap-

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proach which has the potentiality of effecting a major decrease in cancer mortality. This potentiality has not been realized in man; indeed, no compound in use or under study at present offers significant promise of producing cure of human cancer. That there are systemic agents at all which alter the course of some malignant diseases is a signal achievement worthy of full exploitation. Several drugs in current use offer worthwhile benefit to cancerous patients. Close study of these agents may promote synthesis of drugs possessing cancerocidal rather than cancerostatic action, or discovery of compounds better able to provide remissions, if not cures.

Certain characteristics of the several cancer chemotherapeutic drugs permit their classification in different ways. Perhaps the broadest of these classifications describes the mechanism of action as interpreted clinically. Essentially these drugs may be segregated into (*a*) those agents which chiefly effect the host's response to, or toleration of, malignant tissue, with a variable degree of effect on the cancer cells, and (*b*) those agents which exert toxic action directly on cancer tissues, with a variable degree of toxicity in normal host cells.

The antineoplastic effect of the drugs to be discussed, although not cell-specific, is not diffuse nor wholly nonspecific. To a great extent the effect is limited to a certain disease or group of diseases. Without major exception, those malignant growths which currently can be favorably modified by drugs arise from hematopoietic tissues, lymphoid and reticular tissues, and from some of those organs whose functional status is influenced by endocrine control. For the vast majority of individuals with metastatic carcinomas, there is no drug of proven value. Many reasons might be advanced for the failure of response of carcinomatous cells. Surely there are chemical differences between carcinomatous and lymphomatous cells. These may involve such factors as the relative degree of variance from normal cells, the rate of growth, and the ability to tolerate or adapt to modified biochemical environment.

The drugs of clinical value with current applicability in cancer chemotherapy are: the nitrogen mustard compounds, mechlorethamine and triethylene melamine; the folic acid antagonists, a-methopterin and aminopterin; the purine analog, 6-mercaptopurine; the hormones, cortisone and testosterone; and the estrogenic substance stilbestrol. Note will be made of adrenalectomy and hypophysectomy and of some chemical agents of limited clinical importance: urethane, myleran, and the ethylene phosphoramides.

Nitrogen Mustards

Mechlorethamine (HN2) has usually been called nitrogen mustard, the generic name for the entire group of compounds, since its initial use in clinical medicine in 1942 (*9*). It is a highly active compound which forms stable linkages with many constituents of essential biochemical reactions, according to the general schema in figure 1.

Reactions occur with amino groups, carboxyl groups, sulfhydryl radicals, proteins, certain vitamins, purine and pyrimidine compounds, nucleic acids and with many other molecules of biological importance (*10*). The rate of chemical reaction with these compounds is extraordinarily rapid, and within several minutes the drug is fixed to tissue constituents. Most of the effects of such chemical alterations, however, are not manifest biologically until many hours or days later.

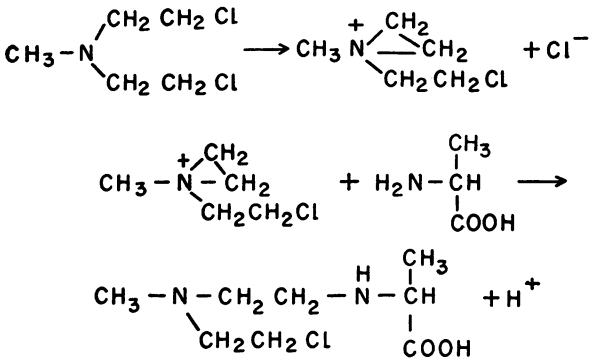
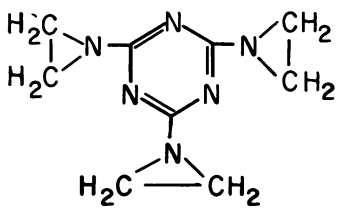


Figure 1. The interaction of mechlorethamine with the amino acid, alanine.

Triethylene melamine (TEM) possesses three ethylenimine groups and participates in reactions similar to those of mechlorethamine. There is no essential difference in their mechanisms of action, nor in their spectrum of anti-

tumor effects. Both nitrogen mustard compounds demonstrate their greatest usefulness in the lymphomas, and each should be employed as a complement to radiotherapy. They do not supplant localized irradiation in the treatment of localized disease. When a lymphoma becomes "active" simultaneously in multiple sites, however, its control by radiotherapy is difficult or impossible. The delivery of sufficient radiation to several involved areas in an attempt to control tumor growth may induce profound marrow suppression or death.

The efficacy of HN2 and TEM is qualitatively the same in Hodgkin's disease and the lymphosarcomas. In the latter, the effects are usually the most striking in giant follicular lymphosarcoma, to a lesser extent in lymphocytic lymphosarcoma, and least in reticulum cell lymphosarcoma. In the course of Hodgkin's disease, fever, pruritis, exacerbations involving multiple node areas, and other indications of generalized disease are common. The administration of mechlorethamine or triethylene melamine is frequently propitious under such circumstances. Decrease or disappearance of tumor masses, beginning even within 24 hours, abolition of fever, relief from itching, and other evidences of clinical remission may follow shortly upon the administration of a nitrogen mustard compound.



Triethylene melamine

The duration of such remission, if it occurs, is extremely variable; although in giant follicular lymphosarcoma remission of generalized disease may persist for months or years, the average duration in Hodgkin's disease and lymphocytic lymphosarcoma is measured in weeks. Radiotherapy may be used to great advantage to effect further regression in important local areas if the response to mechlorethamine or TEM has been suboptimal.

Another indication for mechlorethamine arises when space-occupying or invasive lymphomas have compressed to dangerous extent such organs as the trachea or the spinal cord. An initial vascular reaction with edema, frequently encountered after aggressive radiotherapy, is not seen with mechlorethamine. Intravenous administration of this compound may offer rapid effect in an emergency situation.

It has been stated that the nitrogen mustard compounds are effective in radioresistant lymphomas, that they preserve the sensitivity of a tumor to radiation, and that their use prolongs life in a way different from, and supplementary to, the benefit gained from radiotherapy. There would seem to be little substance to these claims. The apparent effect of nitrogen mustards in lymphomas not responding clinically to radiation is explained by the suppression of many areas of tumor activity simultaneously. In contrast, successive radiation treatments to local areas allow new or continuing tumor activity to flourish in untreated sites. When a tumor mass fails to regress locally under properly directed and adequate radiation therapy, no major regression is to be expected in that area after nitrogen mustard administration (*11*). It has been demonstrated that no difference in survival exists between a group of patients with Hodgkin's disease treated with radiotherapy alone and a group subjected alternately to courses of radiation and mechlorethamine treatment (*12*). The number of radiation treatment days per month in the mustard plus X-ray group was decreased, however, in contrast to radiation alone, thus affording easier clinical management of the patient.

In other diseases, nitrogen mustard compounds give measurable improvement, ranging from major regression of the neoplasm to symptomatic benefit. Because of the convenience of oral administration, TEM is profitably employed in mycosis fungoides, in chronic myelocytic leukemia, in chronic lymphocytic leukemia in small dosage, in metastatic cystadenocarcinoma of the ovary unsuited to other therapy, and in some cases of inoperable bronchogenic carcinoma (*13–15*). Recently, TEM has been found to produce far better results when used in conjunction with X-ray therapy, than X-ray alone in the treatment of retinoblastoma (*16*). There is no convincing evidence that the results of using the nitrogen mustards in sar-

coidosis and the nephrotic syndrome, or in other nonmalignant diseases, justify the procedure.

The toxicity of mechlorethamine is expressed almost immediately in nausea and vomiting, but this manifestation is satisfactorily controlled in most individuals with chlorpromazine. Triethylene melamine is a less serious offender in this respect. Lymphocytopenia followed by granulocytopenia, thrombocytopenia, and anemia is common to both HN2 and TEM administration. The occurrence of severe marrow depression is not infrequent in those patients with marrow replacement by tumor or with suppression of hematopoiesis from prior radiation or chemotherapy. If tumor invasion of the marrow is decreased following the nitrogen mustards, however, hematopoietic improvement may counterbalance the pancytopenia from the drug (*13*, *17*).

Mechlorethamine must be administered intravenously; this is conveniently performed by injecting the drug freshly dissolved in water or saline through the tubing of an infusion already running. Extravasation is highly irritating and venous thrombosis is not uncommon when HN2 is injected directly. The administration of 0.4 mg./kg. as a course of treatment is usually both safe and effective. This may conveniently be done by giving 0.2 mg./kg. on two successive evenings so that heavy nocturnal sedation may also be utilized to inhibit vomiting.

The parenteral administration of TEM would seem to command little advantage over HN2 (*13*). Its oral use, however, is worth while because hospitalizations solely for nitrogen mustard therapy can largely be avoided. When administered to a fasting patient, with 2 gm. of sodium bicarbonate to neutralize the gastric contents, formation of active ethylenimonium ion in acid medium is prevented, and reaction with compounds in the alimentary contents minimized. The use of 5 or 10 mg. of TEM initially, sometimes followed in 10 to 20 days with 5 and rarely 10 mg., has proved entirely satisfactory to achieve a "mustard effect" (*18*). The failure of repeated-dosing regimens (*13*, *19*) to produce early hematopoietic depression, despite the large total doses ingested, probably lies in acidic activation and reaction of the ethylenimonium ion of TEM and consequent failure of absorption of fully active drug. When administered with sufficient alkali, it is likely that such large total doses would prove disastrous.

Folic Acid Antagonists

The association of anemia in chicks with deficiency of dietary substances found in liver, spinach, and yeast was subsequently recognized to represent, in actuality, folic acid (pteroylglutamic acid) deficiency (*20–23*). Granulocytopenia in rats on purified diets was found to be correctible by administering folic acid (*24*). Acceleration of the acute leukemic process in children after administering derivatives of folic acid was described (*25*). The clinical trial of a compound chemically similar to folic acid, but antagonistic to it in a bacterial system dependent on folic acid for growth, was a normal sequence. The improvement in acute leukemia caused by the 4-amino substituted counterpart of folic acid, aminopterin, established the antineoplastic use of metabolic antagonists (*25*).

The 4-amino group is necessary for effective biochemical competition. A-methopterin (recently renamed methotrexate), the 4-amino-10-methyl-pteroylglutamic acid, has become the most widely used of the antagonists because of its clinical suitability. The folic acid antagonists affect many biochemical systems where transfer of single carbon units is involved. The syntheses of purines and nucleoproteins, the activities of several enzymes, the transformations of certain amino acids, and probably many other processes are diminished or interrupted (*26*).

In experimental systems involving mammalian tissues the inhibition exerted by a folic acid antagonist has been found to be irreversible by folic acid itself. Recent study has established, however, that folic acid exists in equilibrium with folinic acid in the body. This more active compound can successfully compete with aminopterin, and it has been suggested that the antagonist irreversibly prevents conversion of folic acid to folinic acid, whereas the antagonism to folinic acid is competitive and reversible (*27*). These relationships are shown in figure 2.

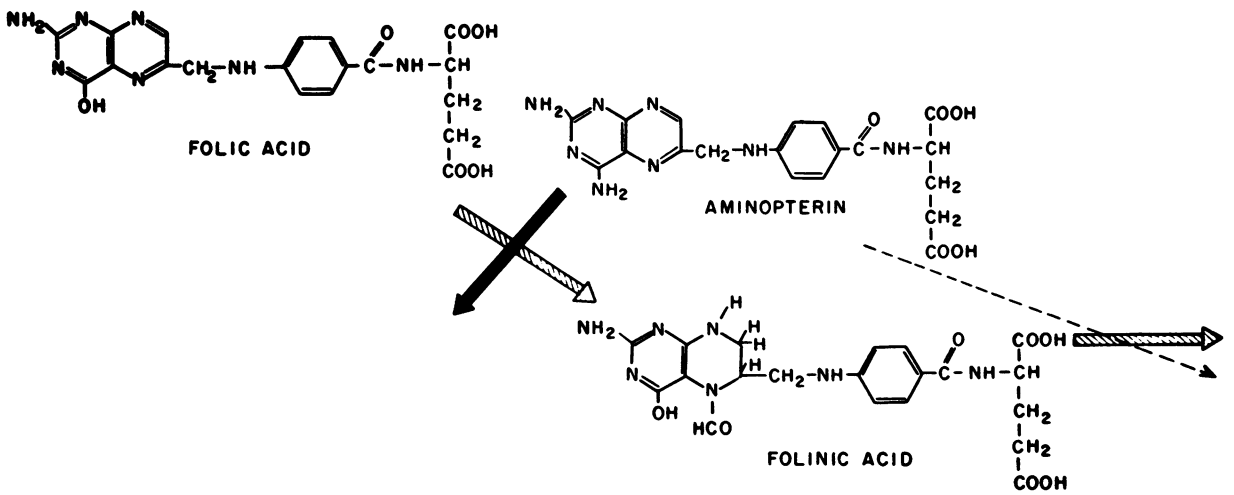


Figure 2. The relation of aminopterin to folic and folinic acids. The shaded arrows indicate normal metabolic pathways. The black arrow represents complete and irreversible antagonism. The interrupted arrow represents competitive antagonism.

In acute leukemia of childhood, the use of methotrexate may result in a temporary cessation of the clinical and morphologic characteristics of the disease. Within a period of 10 to 50 days, one may see disappearance of blast cells in the marrow and peripheral blood, regression of adenopathy and visceromegaly, reestablishment of erythropoiesis, normal leukocyte and platelet production, healing of bone lesions, and clinical well-being. Approximately one-third of those children treated will enjoy a complete or "hematologic" remission, and another one-fifth will sustain appreciable benefit despite the readily demonstrable presence of leukemic cells. The duration of improvement may continue for a few years in isolated instances, but in the average remission, benefit lasts about 10 weeks (*28*).

In the acute leukemias of adulthood, results comparable to those encountered in children are disappointingly rare. Although remissions do occur, only 13.5 percent of 163 adults selected from several reported series experienced any clinical benefit whatever (*28*).

Clinical and morphologic manifestations of acute leukemia reappear at some time during or after folic acid antagonist therapy. Although a second and even a third remission may sometimes be effected by reinstitution or increase of the drug, eventually the disease becomes refractory to folic acid antagonist therapy.

This refractoriness can be exemplified and interpreted by consideration of acute leukemia in rodents. The emergence of resistant strains of leukemic cells which can survive and multiply despite ordinarily suppressive levels of antagonist has been demonstrated (*29*). An understanding of the insensitivity of the cells to antagonists can probably be found in such factors as more efficient absorption and utilization of folic acid, failure of antagonist to gain access intracellularly, better detoxification of antagonist, or alteration of cellular metabolism so that different pathways of synthesis can be utilized when those dependent on folic acid or folinic acid are blocked (*30*). It is probable that eradication of billions of leukemic cells sensitive to an antagonist leaves a residue of preexistent mutant cells insensitive to the drug. When multiplication of these unopposed mutants produces a nearly pure strain of resistant cells, no response to the provoking antagonist can be anticipated. Such insensitivity to folic acid antagonists in leukemic cells is a heritable trait, and strains of transplantable rodent leukemia which have developed resistance are maintained in many laboratories. A similar explanation is probably applicable to human acute leukemia when refractoriness to a metabolic antagonist occurs.

The chronic leukemias are relatively resistant to the folic acid antagonists, and their use in these diseases finds little support in the clinical

literature. The temporary response of neuroblastomas in children to methotrexate administration occurs sufficiently often to make this a reasonable palliative effort. Sporadic and unimpressive response has been reported in a variety of other neoplastic diseases investigated, but in none of these are the results sufficiently encouraging to suggest clinical application.

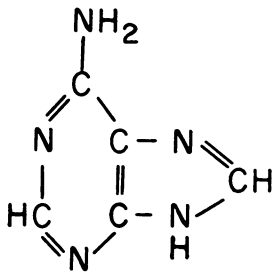
Toxicity is most apparent in those body tissues where rapid cellular proliferation is characteristic. Marrow depression with severe leukopenia, granulocytopenia, anemia, and thrombocytopenia may occur. The epithelium of the alimentary canal is highly susceptible. Anorexia, vomiting, diarrhea, and abdominal pain are often early indications of host toxicity. Ulceration of the oral mucosa, necrosis of interdental papillae and intestinal bleeding are more serious adverse effects. Skin eruptions and alopecia are occasionally seen.

The toxicity of aminopterin or methotrexate is counteracted to some extent by the use of folinic acid (citrovorum factor, Leucovorin). The biochemical competition exerted by folinic acid interrupts the metabolic blockade of the antagonist, and normal chemical pathways are presumably reestablished. A feeling of well-being replaces the malaise and apathy which accompany the toxic state. Remission of the signs of toxicity follows. There is no conclusive evidence that folinic acid per se modifies the acute leukemia (*31*).

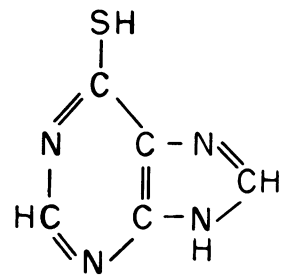
Methotrexate is administered in doses of 2.5 to 5.0 mg. daily, orally. Only rarely are larger daily doses worth while, and then the risk of fulminant toxicity is considerable. The minimum effective dose of folinic acid for relief of methotrexate toxicity is not firmly established. In the range from 10 to 30 mg. daily in divided intramuscular doses, satisfactory results have been observed (*31*).

Purine Analogs

The dominant position that nucleoproteins occupy in cellular metabolism and reproduction has prompted extensive studies of their biochemistry. Nucleic acid is the highly polymerized residue of nucleoprotein after protein has been removed. The constituent moieties of any particular nucleic acid are molecules of phosphoric acid, of a pentose sugar, ribose or desoxyribose, and of a few types of the heterocyclic compounds, pyrimidines and purines. Analogous compounds to the pyrimidine and purine bases have been synthesized (*32*, *33*) in search of metabolic antagonists which could modify the formation of nucleoproteins in cell reproduction and survival. Many antimetabolites active against micro-organisms, malarial parasites, and animal tissues have resulted from these systematic studies.



Adenine



6-Mercaptopurine

The activity of 6-mercaptopurine against certain transplantable animal tumors has been shown to be remarkably efficient (*34*, *35*). Its introduction into clinical medicine in April 1952 was rapidly followed by a definition of its scope of usefulness; to date it is the most practicable of the purine analogs for use in man.

The mechanism of action of 6-mercaptopurine is unknown. It has not yet been proved that 6-mercaptopurine is incorporated into nucleic acids, although much evidence suggests it. Further, if incorporated, it is not known exactly how this is detrimental to the cell. There are physiological compounds of importance other than nucleic acids which contain adenine, such as coenzymes, and it is possible that 6-mercaptopurine exerts antagonism to adenine in these compounds.

Clinically, 6-mercaptopurine demonstrates salutary effects in the acute leukemias and in chronic granulocytic leukemia (*36*). Approximately one-third of the children and a smaller proportion of adults with acute leukemia enjoy major reduction in acute leukemic pathology and symptoms when taking 6-mercaptopurine. A lag period of a few days to several weeks may precede response. When well established, a

remission may progress to disappearance of adenopathy, visceromegaly, and abnormal cells in marrow aspirates. The duration of remissions is usually measured only in weeks or months. Relapse occurs when blast suppression is ineffective. This is explained, as with the folic acid antagonists, by the resistance of the leukemic cells to the biochemical actions of 6-mercaptopurine. Similar resistance phenomena have been demonstrated and studied in murine leukemia (*37*).

In chronic granulocytic leukemia, satisfactory decrease in peripheral white count and visceromegaly can be achieved with 6-mercaptopurine. In the blastic crisis of the acute preterminal phase of chronic granulocytic leukemia, reports of temporary improvement from 6-mercaptopurine have been made. This stage of the disease has been singularly unresponsive to radiation or other chemical agents, and 6-mercaptopurine commands a unique advantage here. In generalized reticulum cell lymphosarcoma, 6-mercaptopurine has produced minor benefit. It holds no significant value for chronic lymphocytic leukemia, the other lymphomas, or in patients with metastatic carcinoma (*36*).

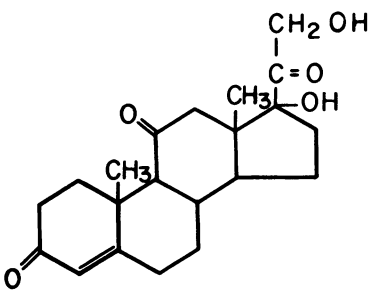
In both experimental and clinical leukemia it has been shown that the inhibitions effected by folic acid antagonists and purine analogs are not biochemically the same. Thus, resistance to an antifolic compound does not preclude sensitivity and response to an antipurine, and vice versa (*36, 37*). The sequential use of these compounds, therefore, offers the possibility of two remissions. There are theoretical advantages to the simultaneous use of both compounds from the start of treatment (*38*), and this area is being explored clinically (*39*).

The toxicity of 6-mercaptopurine is manifest by phenomena quite similar to those of the antifolic compounds. Substantial inhibition of hematopoiesis with resultant pancytopenia may lead to death. In some instances, leukopenia precedes thrombocytopenia and anemia sufficiently to afford warning of impending danger. Gastrointestinal dysfunction occurs less frequently than with methotrexate, but may be equally as severe. Oral ulceration ascribed to the drug has occasionally been seen in patients with acute leukemia. No satisfactory agent for the reversal of the toxicity of 6-mercaptopurine has been used in man. In rodents, several compounds which already contain adenine, such as adenylic acid and adenosine, or guanine, such as guanylic acid and guanosine, are effective in diminishing the effects of 6-mercaptopurine. The purine bases, adenine, guanine, and hypoxanthine, are inferior in allaying toxicity (*40*).

The dose of 6-mercatopurine ordinarily employed is 2.0 to 3.0 mg./kg. daily by mouth. More intensive dosage regimens are said to offer slightly more efficacy, but the toxicity encountered is increased. There is little support for intermittent dosage regimens. Once the drug has been instituted in acute leukemia, discontinuation, except for toxicity or refractoriness, is unnecessary. Sufficient time has not elapsed to judge the optimal methods for use of 6-mercaptopurine in chronic granulocytic leukemia except in its acute terminal phase where continuous administration is practiced.

The Adrenal Cortical Steroids

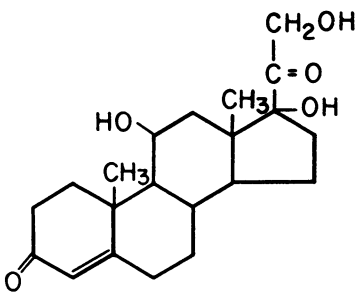
The adrenal cortical steroids, cortisone and hydrocortisone produce qualitatively indistinguishable responses and will not be treated separately. Corticotrophin elicits entirely similar phenomena by inducing endogenous corticosteroid production. Accordingly, cortisone will be used for the generic name.



Cortisone

The response to cortisone has been widely studied in patients with malignant disease. Some apparently specific responses occur in addition to a sense of physical well-being, polyphagia, and elation, which many patients may experience temporarily irrespective of the type of their neoplasm. The most satisfactory specific effect is seen in acute leukemia of child-

hood. With dramatic speed, regression of the signs of disease may occur when cortisone is administered. The swiftness, and to some extent the surety, make cortisone the agent of choice when beginning treatment of a critically ill acute leukemic patient. Cessation of hemorrhage, often before any change in platelet count, and return toward normal hematopoiesis may be evident within a few days. Complete regression of the disease state may follow.



Hydrocortisone

The mechanism of action is unknown. There is a specific effect on the leukemic cell over and beyond the systemic benefits, which is probably akin to the lymphocytolysis seen in normals. The remissions induced are shorter than those from a-methopterin or 6-mercaptopurine, averaging about 6 weeks. If relapse appears while taking adequate cortisone, increase in dosage is but a temporary expedient, and the disease rapidly becomes wholly uninfluenced by the drug. It is in this period of increasing dose and declining antineoplastic activity that the patient may be subjected to intense hyperadrenocorticism.

There is no interrelation of sensitivity or refractoriness to cortisone, 6-mercaptopurine, or a-methopterin. A particular child may enjoy hematologic remission from any, all, or none of these drugs (*36*). No criteria are yet available to predict susceptibility other than clinical trial; accordingly, consideration must be given to clinical management and the choice of antileukemic drug which is to be used first. When the severity of the patient's disease threatens imminent demise or catastrophe, cortisone is best employed, because of its rapidity of action and value in thrombocytopenic hemorrhage, in an attempt to assure survival for a trial of the other drugs. Of the antimetabolites, it would seem safer to begin with methotrexate because folinic acid has at least the potentiality of competing with methotrexate in the event serious drug toxicity occurs.

Uremia, attributable to uric acid crystallization within the kidney, has been described following the use of several different chemotherapeutic agents in instances where extremely rapid tumor destruction ensues. This is a rare complication of acute leukemia when a precipitous fall in leukocytes follows institution of therapy.

Cortisone administration produces considerably less objective evidence of improvement in acute leukemia of adults than of children. Its administration is often attended by some symptomatic benefit, however, which makes it worth while. The lymphocytic leukemias, in chronic or subacute phase, may respond favorably with decrease in leukemic cellular infiltrations and increase in normal marrow function. In a small proportion of patients with Hodgkin's disease or lymphosarcoma, objective diminution in tumor tissue can be demonstrated, and in a larger group, clinical improvement occurs without appreciable change in node masses (*41*, *42*).

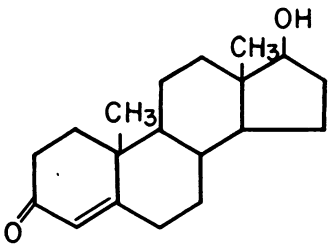
Cortisone often stops bleeding due to thrombocytopenia without increasing the platelet count or modifying the cause of disease in any other way. Decrease in hemolysis associated with splenomegaly in the lymphomas and leukemias may be detected during cortisone administration. Most of these effects are of short duration, but the important temporization afforded frequently allows return of marrow function before a myelotoxic insult is again sustained. Conversely, there is no apparent effect of cortisone on the pancytopenia caused by those drugs toxic to marrow function which are described in this review.

Recently, the use of large doses of cortisone (0.3 gm. daily) in treating metastatic carcinoma of the breast has been reported to produce objective evidence of regression in nearly half the patients (*43*, *44*). Favorable response, where observed, was unrelated to ovarian or adrenal function, since prior surgical removal of these glands did not influence the results. The longest objective remission from cortisone lasted 3 months; symptomatic improvement

also occurred briefly in another third of the patients. At lower doses of cortisone (0.1 gm. daily or less) or with moderate doses of corticotrophin, some subjective improvement, but no objective regression has been seen (*45*).

Testosterone

The sex steroid, testosterone, exhibits its only major application in neoplastic diseases as a treatment for patients with metastatic carcinoma of the breast. A feeling of well-being is experienced by nearly two-thirds of the patients, and oftentimes dramatic disappearance of bone pain allows ambulation in otherwise bedridden women.



Testosterone

Symptomatic benefits far outstrip the objective responses which can be detected by clinical criteria or even by metabolic balance studies. In only 11–19 percent does regression of osseous lesions take place. Effects on soft tissue metastases occur in about 20 percent of cases but are less dramatic clinically than the response of bone disease; pulmonary, cerebral, and hepatic spread are infrequently improved to a significant extent by the administration of androgens (*46*).

The action mechanism of androgenic substances in metastatic breast cancer is unknown. Since clinical improvement is often observed without delay in the continuing growth and spread of the tumor, it is assumed that most of the beneficial effects derive from influences on the host tissues and the host's response to the tumor rather than from effects on the cancer cells per se. The palliation which results from androgen administration is relatively short-lived. (*47*). In one study, of those patients who responded favorably to testosterone, 95 percent did so within 2 months. Reactivation of symptomatology occurred within 6 months in 58 percent and in less than a year in 95 percent (*48*).

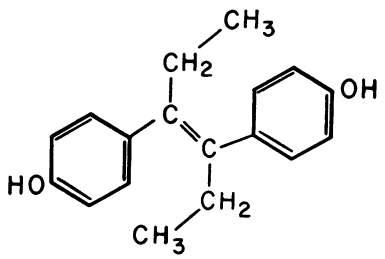
The most widely accepted dosage regimen for the administration of testosterone propionate is 0.1 gm. intramuscularly three times weekly. Larger doses of this compound have been found to offer little except an increased intensity of undesired effects (*46*). These phenomena include voice lowering, hirsutism, acne, edema, flushing, and increase of libido (*49*).

Methyltestosterone can accomplish virtually all the actions of testosterone propionate and is a useful oral therapy (*50*). Chemical hepatitis (*51*), which may occur from methyltestosterone treatment, is an uncommon toxicity that is not prohibitive. Stanolone, a new analog, offers no advantages over testosterone propionate (*52*).

In the presence of osteolytic lesions, any of the androgenic compounds can induce hypercalcemia, presumably through stimulation of the local demineralization process with production of a calcium load in excess of the renal capacity for excretion. Hypercalcemia may be manifested by anorexia, nausea, vomiting, constipation, oliguria, azotemia, apathy, coma, and death. The occurrence of hypercalcemia in approximately 10 percent of the patients treated with androgens must be anticipated (*53*, *54*). No thoroughly satisfactory treatment for hypercalcemia has been advanced (*55*).

Diethylstilbestrol

Diethylstilbestrol and the naturally occurring estrogenic compounds are used with good response in the majority of patients with carcinoma of the prostate, and in carcinoma of the breast of males and postmenopausal females.



Diethylstilbestrol

In males, stilbestrol administration is often a part and prolongation of "androgen control"

therapy which includes initial castration. In elderly females, it is said that estrogen administration changes the hormonal milieu to one alien to the cancer cells. Whether, indeed, stilbestrol has pharmacological antineoplastic actions which are independent of its estrogenic properties is not known. Regression of the primary tumor and soft tissue metastases as a result of stilbestrol therapy in carcinoma of the breast in females may be a dramatic event.

In one study, 90 percent of those patients who responded favorably did so within 2 months. The duration of response produced by estrogens was longer than that from testosterone; 30 percent of the patients were still in remission after 12 months, and 6 percent had not relapsed after 2 years (*48*). Degeneration of tumor cells and cicatrization of the tumor area, far in excess of similar phenomena in untreated cancers, has been demonstrated (*56*).

The association of significant benefit from estrogen administration and postmenopausal status of at least 5 years, without regard to chronologic age, is persuasive. Major tumor regression has been produced in 24 of 99 women 5 years or more postmenopausal, whereas, only 1 of 42 patients below these limits sustained similar regression. Eight of the 42 younger women suffered exacerbation of their cancer from estrogen (*48*). The use of estrogens in this latter group offers considerably less than androgen therapy. For the more advanced postmenopausal patients, however, stilbestrol is the most satisfactory and practicable drug (*46*).

The frequency of osseous metastases in older women is less than that in the physiologically younger age groups where testosterone is usually employed. In these more aged patients, however, equally good regressions of bone metastases are effected by stilbestrol. Nearly one-half of properly selected patients have regression in breast, skin, and lymph node spread, and one-third experience improvement in pulmonary lesions. Other visceral metastases are less responsive (*46*).

The medical management of prostatic cancer, by hormonal means, is more satisfactory than that for any other disseminated carcinoma. Stilbestrol in small doses is capable of prolonging life and palliating symptoms almost as effectively as castration. Extensive data indicate that a combination of castration and stilbestrol administration reduces mortality and morbidity for prostatic cancer more effectively than either method alone (*57*). Decrease in tumor activity evidenced by relief from pain, palpable diminution in, or disappearance of, tumor masses, reduction in, or cessation of, osteoplastic activity of metastases, and a fall in circulating acid phosphatase are among the benefits seen. Restitution to nearly normal health occurs while the tumor is regressive or static. A marked decrease in the extent and cellularity of malignant tissue is noted microscopically, and diagnostic characteristics of carcinoma may be nearly lacking.

The duration of such a remission in patients who have been castrated and given estrogen therapy is appreciable. Thirty-five percent of men with metastases, and 50 percent of those without metastases, at the time of institution of treatment, survive for 3 years (*65*). Eventually, refractoriness to therapy and exacerbation of the disease occur despite administration of estrogen. A possible explanation of this phenomenon could be the tumor's sensitivity to androgens produced by the adrenal cortex (*58*). Temporary benefit in a fraction of the men at this stage of the disease following bilateral adrenalectomy lends some credence to this hypothesis. The lack of objective response in the majority of patients (*59, 60*), however, suggests that adrenal androgenic stimulation is not the essential support for progressive growth. Rather, a state of relative tumor autonomy, without regard to hormonal support or suppression, seems to succeed the condition of the previously dependent cancer in most patients (*7*). Accordingly, adrenalectomy for prostatic cancer has largely been abandoned.

The response of metastatic carcinoma of the male breast to castration, with or without estrogen, is qualitatively similar to the response of prostatic cancer. The frequency, completeness, and duration of objective and subjective response in the few cases reported (*61, 62*) are better than the response of carcinoma of the female breast to oophorectomy or to hormonal therapy.

Many dosage regimens have been advocated for stilbestrol administration in cancer patients.

These vary in the main from 1 to 1,000 mg. daily. A considerable experience has been obtained in the lower dosage range from 1 to 15 mg. per day in divided doses orally. No convincing evidence exists that larger doses accomplish qualitatively or quantitatively different results. The more common undesired effects of stilbestrol are anorexia, nausea and vomiting, fluid retention, breast engorgment (gynecomastia in males), nipple and axillary pigmentation, frequency and incontinence, and interval and withdrawal uterine bleeding. Hypercalcemia while taking stilbestrol has been reported in women with osteolytic metastases from breast cancer (*46*, *49*).

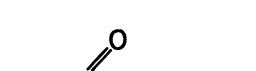
Endocrine Surgery

Many agents and procedures are currently under investigation to determine their place in the medical control of cancer. Of these, one must mention bilateral total adrenalectomy. In certain patients with carcinoma of the female breast, adrenalectomy has been shown to afford objective and subjective remission (*43*, *59*, *60*, *63*, *64*). Evidence has been presented that predictability of the response to operation may be possible. Differentiation of the tumor, in contrast to anaplasia, is reported to be associated with good clinical response (*63*). Others have been unable to confirm this (*43*, *60*). When sensitivity of the carcinoma to administered estrogens has been demonstrated, where such sensitivity or "dependency" is determined by an increase in negative calcium balance in patients with metastatic osteolytic lesions subjected to a challenge course of estrogens, oophorectomy and subsequent adrenalectomy have offered benefit, presumably by removal of estrogen-producing tissues (*43*). The position that adrenalectomy will have in the management of metastatic breast cancer is not yet defined. In the meantime, the extent of the procedure, with the hospital and economic burden entailed, properly limits its indiscriminate empiric use.

Hypophysectomy has been performed by one group on nine patients with carcinoma of the breast. In only a single patient is sufficient data available to assess the response, and she enjoyed moderate benefit (*65*). More recently, objective diminution in osteolysis during the course of metastatic breast cancer has been reported following hypophysectomy in two patients who previously had had oophorectomy and adrenalectomy (*66*). The subsequent administration of somatotropin was associated with metabolic evidence of progression of the disease, reflecting a direct effect of somatotropin on human breast cancer. Other reports of failure to improve patients with malignant melanoma (*67*) and adrenal cortical carcinoma (*68*), together with the magnitude of the procedure (*65*), suggest a reserved and critical evaluation of this operation before it is enthusiastically accepted into surgical endocrine therapy.

Urethane

Urethane is a simple chemical compound first reported in 1946 to be of use in treating the chronic leukemias (*69*). A considerable experience in these diseases has established a place for urethane as a satisfactory alternative to radiotherapy. Continuous administration at levels of 1 to 5 gm. daily may achieve satisfactory response although there is rather wide variation in the dose capable of initiating remission. In 13 patients with chronic myelocytic leukemia, 19 to 134 gm. were required in 11 to 36 days to effect a drop in leukocyte counts to levels approximating 20,000. In chronic lymphocytic leukemia, where response was less regular, even more discrepant results were encountered (*69*). The compound demonstrates no clinical usefulness in the acute leukemias. Anorexia, nausea, and vomiting are prominent side effects, but they may be averted by rectal administration (*65*, *66*). Pancytopenia may result from excessive dosage.



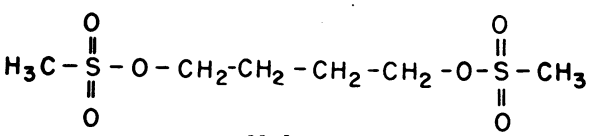
Urethane

The effects of urethane in multiple myeloma are variable. Diminution in plasma cells and myeloma cells in the marrow, decrease in Bence-Jones proteinuria and hyperglobulinemia, relief from bone pain with occasional recalcification, and striking clinical improvement have been de-

scribed (*71–73*). Such amelioration is inconstant, however, occurring in about one-third of the patients with myeloma, and usually persisting for only weeks to months. Radiotherapy directed to painful osseous lesions frequently affords palliation and is a helpful adjunct. The rarity of objective remission from 6-mercaptopurine (*74*) does not support the routine use of this compound in patients with myeloma. Substantial improvement does occur in a fraction of patients treated with ACTH or cortisone (*75*), and these drugs, because of their relative freedom from serious toxicity, seem worthy of trial in a given patient.

Myleran

Myleran is the most active member of a series of aliphatic disulfonic acid esters. This series, because of its chemical resemblance to the nitrogen mustards, was purposefully synthesized in search of compounds with similar biological properties (*76*).



Myleran

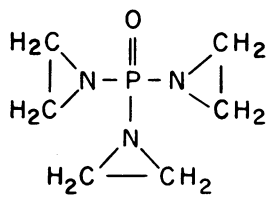
Clinically, myleran has found satisfactory application in chronic myelocytic leukemia (*77, 78*) where fall in leukocyte counts, particularly of immature granulocytes, decrease in splenic size, and rise in hemoglobin follow administration. Lymphocytes are relatively resistant to the action of the drug, but decrease in platelets occurs in virtually all patients and the decrease may continue for many weeks after initiation of treatment. Bleeding may supervene when thrombocytopenia is sufficiently marked.

Wide variation in dosage regimens has been studied. The most satisfactory would appear to be maintenance therapy at about 4 mg. daily, with or without an initial loading dose, in patients checked frequently with blood counts. Under such a treatment regimen, approximately half of the patients with chronic myelocytic leukemia whose treatment has been reported have enjoyed clinical remission and hematological control for 6 months or longer.

Resistance to therapy has been encountered in some patients after initial response. Although patients believed to be refractory to further radiotherapy have responded, in certain instances dramatically, remissions have been rather unsatisfactory and brief when the cell type has been characterized by a higher proportion of myeloblasts, as is frequently the case in the preterminal radioresistant stages of the disease. Acute leukemia has not been benefited (*77, 78*). Although myleran is effective in suppressing many rodent neoplasms, it has been found ineffective in a variety of metastatic human carcinomas (*79*).

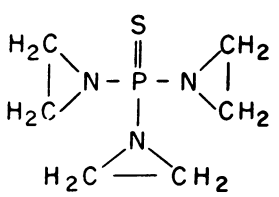
Ethylene Phosphoramides

The actions of mechlorethamine and triethylene melamine in experimental and clinical cancer have stimulated the synthesis and investigation of other compounds which carry ethylenimine groups. Two of the ethylene phosphoramides, triethylenephosphoramide (TEPA) and triethylenethiophosphoramide (thioTEPA) have been subjected to clinical trial.



Triethylenephosphoramide

In rats, TEPA and thioTEPA have a spectrum of anticancer effects similar to one another and to TEM (*80*). In patients with a variety of malignant neoplasms, the results following TEPA administration have approximated those with TEM (*81, 83*). It has not achieved wide clinical application.



Triethylenethiophosphoramide

ThioTEPA has produced satisfactory initial responses in patients with chronic myelocytic leukemia (*84*). Regressions of metastatic carcinomas of the breast and ovary, and of other miscellaneous sites have been reported to occur with considerable regularity following its use by parenteral injection (*84, 85*). Particularly satisfactory remissions have been described after injection directly into a tumor mass.

Inadequate time has elapsed for critical appraisal of this compound by other investigators; the passage of time will also permit evaluation of the duration and clinical value of the response elicited so far. It seems doubtful that intratumor injections should be required if the drug has striking anticancer effects.

Conclusion

The chemical control of cancer has not yet been realized. Within the past 15 years a more profound understanding of cancer has been achieved, and several approaches to its treatment with drugs have been reviewed in this paper. To an appreciable extent, the advances which have been made stem from knowledge and intent rather than from happenstance.

Cancer cells are different from their normal counterparts when viewed under a microscope. Although it is possible that this difference is purely one of rearrangement of the same chemical components within the cell, a vast amount of evidence defines at least quantitative alterations in composition. Functional capacities of malignant and normal cells of homologous tissues may be greatly different. Therapeutic agents which depend on these quantitative differences in the metabolism of cellular constituents afford promise for future progress. A constant search for qualitative differences between neoplastic and normal cells may elucidate obvious pathogenic or perpetuating mechanisms which can be interrupted. Further, it seems within the realm of possibility that pharmacological agents will be found that can effectively counteract the etiological factors which lead to cancer—be they viral, chemical, or physical exposure; idiopathic mutation; or a still unrecognized multitude of cellular insults.

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Joseph Goldberger Award Presented

Dr. Russell M. Wilder, director of the National Institute of Arthritis and Metabolic Diseases, Public Health Service, from 1951 to 1953, recently received the American Medical Association's Joseph Goldberger Award for clinical nutrition. He was cited for his studies of diabetes mellitus and carbohydrate metabolism and for his program for nutrient-fortified foods.

The Joseph Goldberger Award, which consists of a medal and $1,000, is named for the famous National Institute of Health scientist, who was the first to demonstrate that pellagra is a dietary deficiency disease. Dr. Wilder was formerly chief of the department of medicine at the Mayo Foundation. He was a member of the *Public Health Reports* Board of Editors for 1952–53.