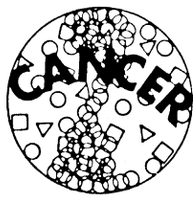
Cancer Chemotherapy: Now a Promising Weapon



Chemicals have made a substantial contribution to cancer therapy during the past 20 years. In 1954, one of every four patients afflicted with cancer could expect to have his survival extended for 5 years or more by effective therapy. Today, the proportion of patients so "cured" has risen to one in three and is still climbing, even if slowly. A substantial fraction of this nearly 30 percent increase in the cure rate, which amounts to 55,000 additional lives saved each year, can be attributed to advances in cancer chemotherapy.

Surgery and radiation are, of course, still the primary forms of cancer therapy. Surgery, the weapon most widely used for a first attack on tumors, is remarkably successful for certain types of malignancies. It is the primary factor responsible for extending survival for 5 years in more than 85 percent of patients with skin cancer, in about 60 percent of women with breast cancer, in about 40 percent of patients with cancer of the colon, and in 70 percent of women with cancer of the uterus.

Radiation is the second most important weapon in the therapist's arsenal; it is particularly useful for treating internal solid tumors if they are detected at an early stage of development. When such tumors are caught early, radiotherapy is responsible for extending survival for 5 years in at least 90 percent of men with one type (seminoma) of cancer of the testis, in at least 80 percent of children with retinoblastoma (a cancer of the eye), in about 75 percent of patients with Hodgkin's disease (a cancer of the lymph system), and in about 50 percent of patients with cancer of the nasopharynx.

Both surgery and radiotherapy, however, have been near the limits of their utility for many years, especially since they are generally useful only against localized tumors. There is some possibility that slight improvements in radiotherapy may result from improvements in focusing the radiation dose on the tumor and from the exploitation of alternative forms of radiation such as fast neutrons and negative π mesons. Nonetheless, the therapeutic efficacies of surgery and radiation are little different from what they were 20 years ago; the only substantive difference is that they are now employed in the treatment of a larger number of patients than earlier.

The situation is substantially different in chemotherapy. In 1954, shortly before the direction of cancer chemotherapy was consolidated in what is now the Division of Cancer Treatment of the National Cancer Institute (NCI), there were perhaps a half-dozen anticancer drugs that were in clinical use, and there were no types of cancer in which drugs could produce substantive improvements in large numbers of patients. Today, there are approximately 40 active drugs that are being used to treat cancer, 10 or so for which clinical testing has recently begun, and another 30 that are in earlier stages of testing. There are also at least 10 types of cancer (out of more than 100) in which it appears that a significant proportion of the patients can have their survival extended by at least 5 years with drugs, and the median period of survival is increasing in a number of others. Progress in the discipline has been relatively slow—some physicians would say agonizingly slow—and there are some crucial stumbling blocks that must be overcome, but the future has never looked brighter or more full of hope.

An Early Poor Reputation

Despite these successes, cancer chemotherapists have a lingering poor reputation among large segments of the lay public. The many apparent failures of chemotherapeutic agents during the 1950's were a bitter disappointment to a public that had rapidly grown accustomed to the "miracle" cures effected against bacterial diseases by the then-recently discovered antibiotics. This bitterness was compounded by the severe side effects associated with many of the most potent anticancer agents, side effects that were frequently given more weight in the public consciousness than the definite palliative effects.

To a great extent, the early failures and the accompanying disappointment resulted from an experimental approach dictated by ethical considerations. The untried anticancer agents could be used only as a last resort in patients for whom all other types of therapy had failed. In most such cases, the patients had already been subjected to surgery, radiotherapy, or both, and the tumor burden was so overwhelming that it was remarkable that the drugs could have any effect at all. All too frequently, friends and relatives of the patients viewed the prolongation of suffering and the side effects of the drugs as a cruel hoax, and that viewpoint has left a residuum of bitterness and skepticism toward chemotherapists. But the investigations of those early years laid a strong foundation for the successes that were to come more recently.

Significantly, many of the earliest successes were obtained with cancers for which the prognosis was most hopeless. These included particularly the leukemias and lymphomas, hemopoietic cancers (cancers of the blood-forming organs) in which malignant white blood cells produced by the bone marrow and the lymph glands, respectively, are disseminated throughout the body. Since these malignancies are generally not amenable to surgery or radiotherapy and were always fatal, chemotherapists were able to initiate treatment as soon as the tumors were diagnosed and, therefore, while the tumor burden was relatively small.

Malignant cells in the hemopoietic cancers also have a growth rate much higher than that of most normal cells (and most tumor cells), and this difference provided the key point of attack. Chemotherapists were thus able not only to treat these malignancies successfully, but also to establish several principles of chemotherapy that have only recently begun to be applied to other types of tumors.

Perhaps the most important of these principles is that chemotherapy has its greatest chance of success when it is applied aggressively against small tumors that have only recently become established; it is much less effective against tumors that are older and larger. This is true whether chemotherapy is the only form of treatment or whether it is used in combination with other techniques. Almost equally important, investigators have shown that appropriate combinations of drugs are, if not synergistic, at least significantly more effective than single agents.

(It is extremely difficult to assign credit fairly for the development of these concepts. In the first place, there is an exceptionally large number of

people working in chemotherapy. Second, the concepts that have proved most important have evolved slowly from the independent work of many investigators. And finally, since many of the tumors that are most susceptible to chemotherapy are among the rarer forms of cancer, clinical trials of promising drugs and treatment regimens frequently require the cooperation of clinicians at many institutions.

Nevertheless, it is possible to select a few names of individuals who have played crucial roles in establishing the principles of combination chemotherapy, early chemotherapy, and chemotherapy as an adjuvant to other types of treatment. These would include: Emil Frei III of the Children's Cancer Research Foundation, Boston, Massachusetts; Emil J. Freireich of the M. D. Anderson Hospital and Tumor Institute, Houston, Texas; James F. Holland of the Mt. Sinai School of Medicine, New York City; Joseph H. Burchenal of Memorial Sloan-Kettering Cancer Center, New York City; Howard E. Skipper and Frank Schabel, Jr., of the Southern Research Institute, Birmingham, Alabama; and C. Gordon Zubrod, Abraham Goldin, Paul P. Carbone, and Vincent T. DeVita, Jr., of NCI, Bethesda, Maryland.)

There are a number of substantive biological differences between old and young tumors that explain why older tumors are more refractory to chemotherapy; many of these differences have been elucidated by Skipper and Schabel. Perhaps the most important difference is that most of the cells in a very young tumor are continually passing through

Screening for Drugs: A Massive Undertaking

The search for anticancer drugs is without doubt the largest organized screening program ever undertaken. In the last 20 years, the National Cancer Institute has underwritten the testing of some 300,000 different chemicals to identify the approximately 50 agents that are now either in use or in clinical testing. Rising costs had slowly reduced the number of chemicals tested yearly to about 15,000 only 2 years ago, but the number tested is now up to nearly 50,000 per year. This increase stems, in part, from increased funds made available by the National Cancer Act of 1971. But it has also been made possible by the recent implementation of the so-called "mini" and "econo" screens.

The fundamental precept on which the new screens are based is that results with two types of sensitive, transplantable mouse leukemias, called L1210 and P388, are so reliable and reproducible that preliminary screening can be accomplished with far fewer animals. (The L1210 leukemia is used for primary screening of most compounds, but the more sensitive P388 is used for screening natural products.) This screening program, designed primarily by Abraham Goldin and Nathan Mantel of NCI, not only greatly lowers the cost of screening, but also makes it possible to work with much smaller amounts of the chemical to be tested. With the mini screen, for example, it is possible to perform an assay with as little as 3 milligrams of material and as few as 20 mice; the old screening system required a minimum of 65 mg of material and at least 40 mice.

A positive result in the preliminary screen is defined as an average 25 percent increase in the life-span of the mice. If a chemical gives a confirmed positive result, as do fewer than 1 out of every 100, it is then tested in mouse lung tumors and skin tumors that are less susceptible to chemotherapeutic agents. A summation of the increased life-spans of mice with the four types of tumors is then used to predict the effect of the drug against human tumors. About 1 out of every 1000 agents tested passes this stage. Those that pass, however, must still undergo extensive toxicological and other testing before they can be tried in humans.

The chemicals subjected to the screening procedure can be divided into seven major classes:

► Compounds that are analogs of known effective agents. A good example is provided by daunorubicin, a glycoside antibiotic that is thought to act by binding to DNA to block its transcription into RNA. Daunorubicin is isolated from *Streptomyces peucetius*, and scientists at the Farmitalia Company in Milan, Italy, found that an artificially produced mutant of this microorganism provides an analog that is hydroxylated at one of its carbon atoms. This analog, adriamycin, is one of the most promising antitumor agents now in use, but it is toxic in that it alters heart action when the cumulative dose exceeds a certain level. Scientists are now looking for analogs of adriamycin that retain the antitumor activity but not the cardiac action.

► Chemicals developed through biochemical, chemical, cell cycle kinetic, pharmaceutical, and pharmacological concepts. Perhaps the greatest activity in this area involves the search for inhibitors of reverse transcriptase, an enzyme that is crucial to the activity of RNA tumor viruses. This search is proceeding even though viruses have never been shown to cause cancer in humans.

► Compounds selected from structure-activity relationships. An example of chemicals developed by this approach is provided by the nitrosoureas, such as BCNU, which have proved to be very effective in treating certain types of tumors.

► Compounds with new structural features that have not been studied.

► Compounds showing antitumor activity in programs outside NCI.

► Compounds isolated from natural sources. Interest in these compounds had died off somewhat as more emphasis was placed on the rational design of antitumor agents, but some scientists feel there has been an upsurge in interest in the last couple of years as the result of the discovery of several promising agents such as maytansine, an alkaloid isolated and identified by S. Morris Kupchan of the University of Virginia, Charlottesville.

► Unsolicited compounds.

The highest priority for testing is given to unstable materials that can be stored for only a short time. Priority is then given, respectively, to compounds found to have clinical activity by outside investigators, compounds with characteristics superior to those previously tested, compounds developed or acquired at the request of NCI, and all others in the order of receipt.—T.H.M.

the mitotic cycle for replication—that is, the young tumor has a large fraction of actively growing cells. Since most current antitumor drugs act by interfering with this cycle (Fig. 1), this large growth fraction makes the cells highly susceptible to the killing effects of antitumor drugs. In older tumors, in contrast, there is a much smaller growth fraction and the tumor is much less susceptible to chemotherapy.

There are also proportionately many more dead cells in a larger tumor; these cells release metabolites that may fuel adjacent viable cells, and inhibit the action of antimetabolites, a class of antitumor agents that interfere with the metabolism of malignant (and some healthy) cells. And finally, the older the tumor, in general, the more debilitated the patient is; his defense systems are thus less able to assist in fighting off the tumor, and he is less able to tolerate the drug.

The inescapable conclusion, then, is that chemotherapy should be initiated while the tumor is young in order to have the best chance of success. This conclusion has been readily accepted in those types of cancer for which chemotherapy is the primary treatment.

But there has been a great reluctance to use supplementary chemotherapy in those types of cancer where surgery and radiotherapy are the primary forms of treatment. To a large extent, this attitude stems from an understandable reluctance of physicians to give toxic drugs to apparently healthy patients in whom all detectable traces of tumor have been eradicated. Yet in many types of cancer, there is strong evidence that these apparently healthy patients are not free of malignant disease.

The most devastating aspect of cancer is the ability of tumors to metastasize: malignant cells are detached from a tumor and carried by the circulatory and lymph systems to other sites in the body, where they establish small pockets of disease. Since tumors are generally not clinically detectable until they contain at least 10^9 cells, one or more undiscerned metastases might remain in the patient when the primary tumor is eradicated by surgery or radiation. It is the complications associated with the subsequent growth of these metastases that are responsible for the majority of cancer fatalities. A growing number of clinicians, consequently, have begun arguing that these metastases should be attacked aggressively with chemotherapy before they are clinically detectable and while they are still most susceptible to drug treatment.

This type of adjuvant chemotherapy has been attempted in the past—particularly in breast cancer patients in the late 1950's—with generally disappointing results. Some scientists, such as Memorial Sloan-Kettering's Burchenal, argue that those failures were due mainly to the use of relatively inactive drugs given for too short a time and in inadequate doses. The current knowledge of treatment regimens, he insists, gives adjuvant chemotherapy a much greater potential for success.

A major problem, however, is identifying those high-risk patients for whom the potential benefits of chemotherapy outweigh the risks. The need for such an identification is one explanation for the intense interest in the development of sensitive assays for the detection of biochemical markers or of fetal and tumor antigens (*Science*, 12 April, p. 147) from tumors that would otherwise be undiscernible. Such assays would also be extremely useful in monitoring the course of chemotherapy. Their development, argues NCI's Zubrod, director of the institute's Division of Cancer Treatment, would do more to speed the chemical control of cancer than any other single technique. In the interim, however, clinicians are forced to rely on past experiences to predict which patients are the best candidates for adjuvant chemotherapy. Typically, these have been patients in which a fatal recurrence was a foregone conclusion. Good examples of the recent successes of aggressive chemotherapy against such malignancies are provided by results with several childhood tumors, including Wilms' tumor, embryonal rhabdomyosarcoma, and osteogenic sarcoma.

Wilms' tumor is a lethal cancer of the kidney of children. Treatment with either surgery or radiation has produced cure rates (2-year survival) no

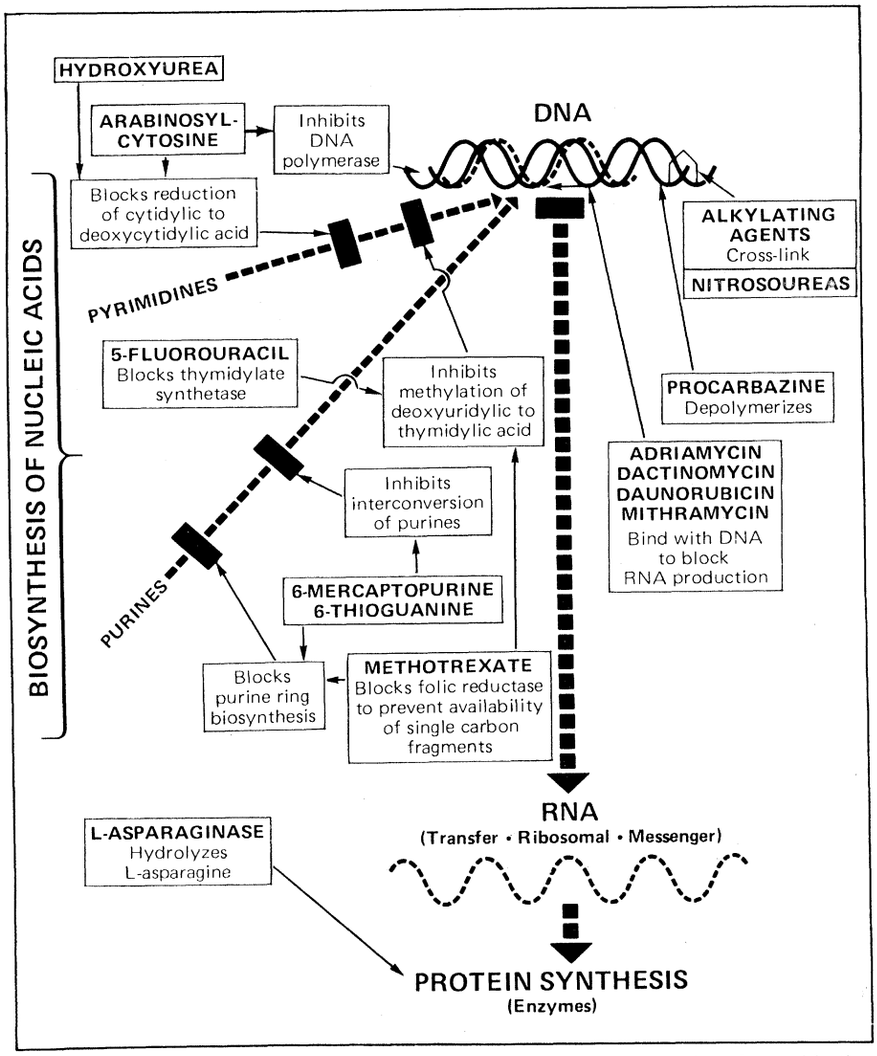


Fig. 1. The mechanism of action of several antitumor agents that interfere with the replication of cells. [Source: Irwin H. Krakoff, Memorial Hospital for Cancer and Allied Diseases, New York City]

higher than 23 percent; a combination of the two increases the rate to 40 percent. But the late Sidney Farber and his associates at the Children's Cancer Research Foundation have shown that the cure rate can be increased to more than 80 percent if surgery and radiotherapy are followed by treatment with the antitumor antibiotic actinomycin D.

Embryonal rhabdomyosarcoma, a muscle tumor that generally appears soon after birth, exhibits much the same responsiveness to surgery and radiation as Wilms' tumor, but is less sensitive to chemotherapy. Nonetheless, Charles B. Pratt III of St. Jude Children's Research Hospital in Memphis, Tennessee, Sarah S. Donaldson and J. R. Wilbur of Stanford University School of Medicine in Palo Alto, California, and Fersteh Ghavimi of Memorial Sloan-Kettering have shown that surgical removal of the bulk of the tumor, radiation therapy to all known areas of disease, and as much as 2 years of chemotherapy with a combination of vincristine, actinomycin D, and cyclophosphamide appears to produce long-term, disease-free survival. Donaldson and Wilbur report that 14 of 19 patients have no evidence of disease 3 to 10 years after the start of therapy; Ghavimi has obtained similar results in 21 of 25 patients observed for as long as 3 years.

Osteogenic sarcoma is a children's bone tumor that more closely resembles adult tumors in its resistance to treatment. The most widely used therapy, amputation of the affected limb, has prolonged survival for 5 years in less than 20 percent of patients; more than half the patients have lung metastases within 5 to 9 months after surgery. In a unique approach based on earlier work by NCI's Goldin and Isaac Djerassi of Mercy Catholic Medical Center in Darby (Philadelphia), Pennsylvania, it has been shown by Norman Jaffe and Emil Frei of the Children's Cancer Research Foundation that metastases can apparently be prevented by massive doses of the antimetabolite methotrexate followed by administration of a compound called citrovorum factor. Methotrexate is an analog of folic acid, a vitamin that is the source of single-carbon fragments in the synthesis of purines for DNA; it inhibits an enzyme called folic acid reductase, and thus impairs replication of malignant and, to a lesser extent, healthy cells. It is one of the most widely used antitumor agents, but it can be used in only limited quantities because of its toxicity to normal cells.

Djerassi has shown, however, that methotrexate can be used in quantities 100 times as great as the normal dose provided that the patient's healthy cells are "rescued" within 6 to 12 hours by citrovorum factor. Citrovorum factor is another folic acid analog that, in essence, substitutes for the normal product of folic acid reductase, thus bypassing the inhibited enzyme. For reasons that are not yet totally understood, this combination of drugs does considerably more damage to malignant cells than to healthy ones. Jaffe's preliminary evidence shows that, of 12 patients treated in this fashion, 11 show no metastases as long as 18 months after amputation.

Some progress in treating osteogenic sarcoma is also being made with other drugs. E. P. Cortes of Queens Hospital Center in New York City has reported that 14 of 15 patients treated with radical surgery and adriamycin show no evidence of metastases for as much as 26 months after amputation. And Wataru W. Sutow and his associates at M. D. Anderson have reported that 10 of 18 patients treated with a combina-

How Do Antitumor Agents Act?

Antitumor agents can be divided into at least six classes that reflect their varying mechanisms of action. These classes include the steroidal hormones, alkylating agents, antimetabolites, antibiotics, specific mitotic inhibitors, and miscellaneous drugs.

The era of modern cancer chemotherapy began in the early 1940's when Charles Brenton Huggins of the University of Chicago first used estrogen, one of the *steroidal hormones*, to produce remissions in cancers of the prostate. Other hormones, such as cortisone, prednisone, progesterone, and several androgens, have subsequently been found useful in treatment of some cancers arising from tissues particularly susceptible to hormonal influences. The mechanism of action of the hormones is not yet understood, but it is possible that they interfere with cell membrane receptors that are involved with the stimulation of growth.

Nitrogen mustard, an *alkylating agent*, was one of the first synthetic chemicals to show antitumor activity. The alkylating agents are generally, but not always, polyfunctional, and are thought to act by cross-linking cellular DNA, thereby impeding its ability to act as a template for RNA synthesis. Other members of this class include chlorambucil, cyclophosphamide, the nitrosoureas, and the imidazole carboximides.

The *antimetabolites* interfere with the biosynthesis of nucleic acids by substituting for normal metabolites in certain enzymic reactions and inhibiting the enzyme. The most important of these are methotrexate, first synthesized by Lederle Laboratories, Pearl River, New York; 5-fluorouracil, synthesized by Charles Heidelberger of the McArdle Laboratory for Cancer Research, Madison, Wisconsin; and 6-mercaptopurine, synthesized by George Hitchings of Burroughs Wellcome Company, Research Triangle Park, North Carolina. More recent members of the class include arabinosylcytosine, thioguanine, and 6-azauridine triacetate.

The *antibiotics* are complex, naturally occurring compounds produced by microbial fermentation. Some, such as daunorubicin, actinomycin D, and adriamycin are thought to bind nonspecifically to cellular DNA, thus interfering with its transcription. The mechanism of action of others, such as bleomycin and streptozotocin, is not yet known.

The important *mitotic inhibitors* are the vinca alkaloids vincristine and vinblastine. They destroy the mitotic spindle, thereby halting cell division.

The *miscellaneous* drugs do not fall into any of the previous categories. L-Asparaginase, for example, hydrolyzes asparagine in the blood; certain types of tumor cells require an external source of asparagine, and this enzyme blocks that source. Hydroxyurea, while not strictly an antimetabolite, works like one in that it inhibits the enzyme ribonucleoside diphosphate reductase, thus blocking the conversion of cytidylic acid to deoxycytidylic acid, an essential component of DNA. And procarbazine, a methyl hydrazine derivative, depolymerizes cellular DNA.—T.H.M.

tion of adriamycin, cyclophosphamide, vincristine, and L-sarcolysin have been free of disease for periods of 19 to more than 24 months. Results with Sutow's patients, who have survived the longest of any reported above, intimate that chemotherapy is doing more than simply delaying the onset of metastases.

These data and comparable results with other tumors of children suggest that aggressive chemotherapy which may be only temporarily palliative with a large tumor mass may be curative when there is only a small amount of tumor left after surgery or radiotherapy. Buoyed by their results with the tumors occurring in childhood, investigators are now planning and implementing clinical trials in which multifaceted therapy will be applied to some of the major cancers of adults, including tumors of the breast, lung, and colon. Because recurrences are often naturally delayed for extended periods, however, definitive results will probably not be available for several years.

Another point illustrated by the previously discussed results is the importance of combinations of drugs in treating many types of tumors. Most antitumor agents, as has repeatedly been stressed, have varied side effects associated with their toxicity to healthy cells. Most drugs that interfere with the replication of malignant cells, for example, also kill normal cells that have a high growth fraction—such as cells of the gastrointestinal tract and the bone marrow. These agents thus produce effects ranging from nausea and hair loss to suppression of the immune system. Adriamycin, a promising antibiotic, causes cardiac problems when the cumulative dose exceeds a certain amount. Vincristine, a vinca alkaloid that halts cell division by destroying the mitotic spindle, is toxic to peripheral nerve cells. And bleomycin, one of the few agents that does not suppress bone marrow, is toxic to lung tissue.

Proper design of combination chemotherapy, says Paul Carbone of NCI, involves selection of drugs with both different toxicities and different mechanisms of action. Each drug can then be given in a full dose: the antitumor activities will be additive, but the toxicities to normal cells will not. An additional requirement is that therapy be intermittent so that the normal cells and the immune system may have a chance to recover.

Carbone and DeVita first applied these concepts to Hodgkin's disease when they used a combination of nitrogen mustard, vincristine, procarbazine, and prednisone. This combination, known by the acronym MOPP, more than quadrupled the number of patients who went into complete remission. MOPP has subsequently been adopted by most clinicians for the treatment of Hodgkin's disease, often in combination with radiotherapy. Similar regimens developed by Frei, Freireich, and Holland for acute leukemia have increased the incidence of long-term survival in that disease from 0 to more than 50 percent.

Some Regimens Complicated

Some of the most recent treatment programs can be quite complicated. Norma Wollner and her associates at Memorial Sloan-Kettering, for instance, have reported striking results in the treatment of advanced non-Hodgkin's lymphoma with an intricate combination of drugs. Therapy begins with massive doses of cyclophosphamide, followed by radiotherapy to any localized lesions, and a regimen that has also been successfully used in the treatment of acute lymphoblastic leukemia: Vincristine, prednisone, and daunomycin are given to induce a remission, and are followed by methotrexate to prevent central nervous system involvement, short courses of arabinosylcytosine and thioguanine, twice-weekly doses of L-asparaginase for 4 weeks, a single dose of BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea], and then 6-week cycles of an equally complicated maintenance therapy. Of 35 patients treated with this regimen, 28 still have no evidence of disease after 9 to 34 months. In contrast, 14 of 18 patients previously treated by Wollner with repeated large doses of cyclophosphamide had recurrences of the lymphoma at a median interval of 4 months.

The further application of the concepts developed in the treatment of hemopoietic malignancies and childhood tumors makes the future of chemotherapy against solid tumors look very promising. There are, though, a number of impediments. Perhaps the most important is simply the large number of available agents and the larger number of cancers against which they must be tested. Of the 29 most promising antitumor agents, for example, more than half have been adequately tested in only 4 of the 16 most widely fatal tumors. In the remaining 12 major tumors, the percentage that has been tested varies from 17 to 45. There is, moreover, a backlog of promising agents that have never been tested in humans at all. One of the most frequently repeated criticisms of NCI, in fact, is the apparent slow speed at which many potentially curative drugs are moved through the screening and testing processes. Many of these complaints are directed toward the fact that a year or more of toxicological testing must be performed before a new drug can be used in humans; but Zubrod argues that shortcuts in this testing are absolutely inappropriate when the safety of patients is at stake. He further argues that the rate of appearance of new anticancer agents has increased significantly in recent years.

Another problem that has begun to be recognized is an increased incidence of second, apparently unrelated tumors in patients who have been cured of cancer. Of 438 patients treated for Hodgkin's disease at NCI, for example, 14 later developed other types of tumors—a rate that is three to four times the expected incidence for those patients. This increased susceptibility to tumors appears to result from the action of radiation and certain antitumor agents that are thought to be carcinogenic; among patients who received both intensive radiation and suspected drugs, the incidence of second tumors was about 25 times the expected rate.

An alternative explanation is that suppression of the immune system by radiation and antitumor drugs makes the patient more susceptible to other carcinogens. This possibility is supported by recent observations by Israel Penn of the University of Colorado, Boulder, of an increased incidence of tumors among transplant patients who have received immunosuppressive drugs. In any case, though, it must be remembered that most of the cancer patients in whom the second tumors develop would have been dead long since were it not for the anticancer therapy. The use of potentially carcinogenic therapy thus unquestionably seems justifiable.

A final problem, albeit one that is rapidly disappearing, is the lack of regard for chemotherapists that has historically been exhibited by many surgeons and radiologists. If any one principle has been most firmly demonstrated by recent research in cancer chemotherapy, it is that practitioners from each of these three disciplines must work together very closely if there is to be a significant improvement in the survival of high-risk patients.—THOMAS H. MAUGH II