The National Cancer Chemotherapy Program

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In 1955 the U.S. Congress authorized $5 million for the National Cancer Institute (NCI) to establish a Cancer Drug Development Program. This remains a major program at NCI. It was and continues to be of concern both within the scientific community and the lay press, as evidenced by a recent series of articles in the Washington *Post*. It is timely, therefore, to review the program with respect to progress, perspectives, and problems.

Summary. The National Cancer Chemotherapy Program was initiated in 1955. It is administered and integrated by the Division of Cancer Treatment at the National Cancer Institute. The program involves the discovery and development of potential new antitumor agents; their screening in preclinical experimental systems for antitumor effect, and, if active, for toxicology; and, for selected agents, preliminary, and more definitive clinical trials. While serendipity and empiricism played a substantial role in the early years of the program, the program has increasingly emphasized and been influenced by advances in tumor biology, drug development, clinical pharmacology, and the science of clinical trials. There has been effective interaction between investigator-initiated research on the one hand and developmental research at preclinical and clinical levels on the other. Over 30 chemotherapeutic agents with substantial clinical antitumor activity have been discovered, and their proper use, often in combination and often integrated with surgery or radiotherapy, has resulted in significant progress in the effective treatment of many forms of cancer.

Factors that influenced the initiation and large-scale support for the program include the following.

1) The need for systemic treatment for cancer. Advances in surgery and radiotherapy have been such that curative treatment can be delivered to many patients whose tumor has not spread beyond the local and regional lymph-node–bearing areas. Of the 785,000 new patients with cancer (excluding the highly curable squamous and basal cell carcinomas of the skin) annually in the United States, 30 percent fall into this category. Cancer prevention and early detection techniques may improve these figures, and priority has been given to such research. For the 550,000 patients whose disease has spread beyond the local or regional area, major advances in treatment, and particularly curative treatment, require systemic therapy (*1, 2*). This includes chemotherapy, hormone therapy for endocrine-dependent tumors, and immunotherapy.

2) The observation in 1943 that nitrogen mustard, a congener of the war gas sulfur mustard, was capable of producing tumor regression in patients with lymphoma and the discovery, in 1947 and 1955, respectively, that the folic acid antimetabolites produced temporary remissions in childhood leukemia and a cure in patients with choriocarcinoma (*3–5*).

3) The development of the science of pharmacology and its application to a variety of areas, including, for example, the highly successful programs of screening and development of antibiotics for the control of infectious diseases and the "crash" program for the development of antimalarial compounds during World War II.

4) The development of transplantable animal tumors in syngeneic hosts and therefore the potential for quantitative drug assessment (*6*).

5) The control of infectious diseases and the emergence of cancer as the second major cause of death in the United States (after cardiovascular diseases).

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The Drug Development Program

The drug development program has undergone changes and refinements over the past 27 years. It is currently organized within and integrated by NCI's Division of Cancer Treatment. The director of this division runs the drug development program as advised by a Board of Scientific Counselors. The division has an intramural, multidisciplinary clinical program, as well as a developmental therapeutics program which includes laboratory efforts in biochemistry, medicinal chemistry, and pharmacology. It also integrates resource contracts for, for example, drug acquisition and pharmacology and monitors and serves as a resource for extramural investigator-initiated cancer therapeutic research.

A linear array system was organized for new drug development, which included the following stages: (i) the acquisition of new compounds, (ii) screening*, (iii) production and formulation*, (iv) toxicology*, (v) phase I clinical trials*, (vi) phase II clinical trials, and (vii) phase III and IV clinical trials.

The key decision points in the linear array, where rather precise criteria must be met before a drug can advance from one stage to the next, are indicated by the asterisks between the various stages of drug development. An affirmative decision for a particular drug at each point commits large amounts of the division's resources to the development of that drug. These decisions are made by a 30-member Decision Network Committee, which includes intramural and extramural scientists and support staff. In addition, ad hoc and permanent members of the committee serve as "drug advocates" to facilitate the development of a high-priority drug, whether it derives from the screening program or has entered the system through industry or investigator-initiated research. Subcommittees provide advice on and facilitate the synthesis and development of analogs of antitumor agents with established activity (*2, 7, 8*).

The Acquisition of New Compounds

Drug development begins with the selection and acquisition of agents for screening. Compounds enter the program through voluntary submissions and by solicitations of the pharmaceutical industry, universities, research institutes, government agencies, and NCI's intramural program. Continuous literature surveillance on the basis of relevant

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chemical, pharmacologic, and biologic criteria, is also used to select new drugs.

The relative role of the NCI program (intramural and contract-supported) of investigator-initiated research in academia and of the pharmaceutical industry are difficult to dissociate, particularly with respect to the identification of active agents. The NCI role has been primarily developmental. It has provided stimulus, support, and scientific contributions to the program and has been responsible for the integration of efforts in drug development, preclinical screening, toxicology, clinical pharmacology, and quantitative clinical trials. Most of the original observations have come from investigator-initiated research (usually with grant or contract support from NCI). Finally, particularly in recent years, the drug industry has become extensively involved in the synthesis and development of cancer chemotherapeutic agents, particularly in the area of chemical analogs.

From 1955 to 1975 up to 40,000 agents per year were selected for screening, largely on an empirical, random basis. After 1975 the number of compounds was reduced to less than 15,000 per year by the more rational development of agents. This was made possible by prior experience and particularly by further developments in medicinal chemistry, pharmacology, and tumor biology (*2, 8*).

The 700,000 compounds and extracts that have been acquired and screened by the National Cancer Chemotherapy Program since 1955 may be broadly categorized as follows.

Chemical synthetics. These include some 350,000 compounds, most of which were acquired empirically in the early years of the program. Only a minority of the agents fall into identifiable classes of antitumor drugs. These include the alkylating agents and antimetabolites.

The prototype alkylating agent is nitrogen mustard, which was discovered during World War II (*3*). Ten thousand alkylating agents have been synthesized in an effort to improve their antitumor activity, on the one hand, and to lessen toxicity on the other. These studies have resulted in the development of alkylating agents with substantially greater stability that can be given by mouth, a major practical advantage (for example, chlorambucil and busulfan). Alkylating agents that have carrier moieties that might direct the compounds more selectively to certain tumors have been synthesized. This has been based on such biological differences as enhanced protein synthesis for myeloma (phenylalanine mustard), enzyme content (cyclophosphamide), and selective tissue toxicity (streptozotocin). While the original biochemical hypotheses in many instances were not verified, the above agents have a substantially different spectrum of antitumor activity and toxicity from each other and from the original nitrogen mustard. The nitrosourea group of alkylating agents are more lipid-soluble and hence they more effectively pass the blood-brain barrier. They are effective in the treatment of brain tumors. They also have substantially greater activity against mitotically resting cells and thus are more active against slow-growing tumors, such as breast and colon cancer in laboratory animals (*9*).

A large number of analogs of metabolites (antimetabolites) known or thought to be important to the survival of tumor cells have been synthesized. These include the various vitamins, amino acids, purines, pyrimidines, and nucleosides. The early development of the folic acid and purine analogs gave major impetus to the antimetabolite area (*4, 10*). In many areas investigator-initiated research provided a major scientific advance whose development and application was facilitated by the National Cancer Chemotherapy Program. For example, when it was appreciated that methylation of the 5-carbon position of uracil was essential for thymidine and DNA synthesis, 5-carbon substituted pyrimidine antimetabolites were developed, of which the most important was 5-fluorouracil. After metabolic activation, 5-fluorouracil inhibits thymidylate synthetase and is also incorporated into RNA (*11*). 5-Fluorouracil has major experimental and clinical antitumor activity. A number of purine and pyrimidine nucleoside analogs have been developed, of which clinically the most important is arabinosyl cytosine, which is exclusively active against the DNA synthesis phase of the cell cycle. Of the antitumor agents with established clinical activity, six are antimetabolites.

Conceptual and methodological advances in recent years provide improved approaches to enzyme inhibition of substrate analogs. Irreversible enzyme inhibition can be achieved by mechanism-based (suicide) inactivators (for example, difluoromethyl ornithine). Reversible inhibition results from transition state analogs (for example, deoxycoformycin) and multistage inhibitors [for example, *N*-(phosphonacetyl)-L-aspartate] (*12*). These three examples are currently being evaluated in clinical trials.

The heavy metals have recently been emphasized in the chemical synthetic area. In experiments conducted for an entirely different purpose, it was observed that a platinum coordination compound released from electrodes in electrolysis experiments produced morphologically distinct antibacterial effects. These complexes were isolated and tested for antitumor activity experimentally, and *cis*-diamminedichloroplatinum II (cisplatin) was subsequently shown to have substantial activity in a variety of human tumors (*13*). Twenty-five hundred additional platinum and other heavy metal coordination compounds have been synthesized. Several of the newer platinum compounds have less nephrotoxicity experimentally than the parent compound and are being evaluated in clinical trials.

Fermentation products. Approximately 200,000 fermentation products have been acquired by the National Cancer Chemotherapy Program. With the demonstration that highly effective antibiotics for infectious disease were produced by soil fungi, these began to be screened for antitumor activity in cancer cells in culture. Initially, crude extracts of a given organism (usually a member of the genus *Streptomyces*) were screened against cells in culture and in transplanted tumors in rodents. If antitumor activity was demonstrated, the active ingredient was isolated. Waksman discovered the clinically active antibiotic actinomycin D in 1952 (*14*). In the past 10 to 15 years, several antibiotics with major clinical activity have been identified. These include the anthracyclines adriamycin and daunorubicin, which were discovered in Europe, and bleomycin, mitomycin C, and other antibiotics discovered and developed largely in Japan. Many of the antibiotics (actinomycin D, the anthracyclines) are multicyclic, planar compounds which intercalate into DNA and inhibit DNA replication and transcription (*8, 15, 16*).

Plant products. One hundred and twenty thousand plant extracts have been prepared from 35,000 different species obtained largely through the U.S. Department of Agriculture from worldwide sources. Some were selected because of folklore evidence that they had medicinal value. The extracts were screened and, if positive, sent to chemists supported by NCI contracts for isolation and purification. In the early 1960's this area received a major boost with the discovery that products of the periwinkle plant, vincristine and vinblastine, had major, clinically useful antitumor activity (*17*). While many new novel alkaloids have been discovered and several have reached clinical trial (bruceantin and maytansine), the plant product

program has been disappointing in terms of identifying active agents and has been scaled down. Semisynthetic derivatives of known active plant products, such as VP 16 (from podophyllotoxin) and vindesine (from vinblastine) have been prepared and have been found to be active in the clinic (*8*).

Marine animal products. Sixteen thousand marine and other animal products and extracts have been screened. However, only extracts of a tunicate have proved to be of interest experimentally, and no such products have reached clinical trial. This area is also being deemphasized.

Biological response modifiers. In the past several years, NCI has developed a major program relating to biological response modifiers. These include (i) agents that modulate the immune system, such as bacterial products, interferon, thymosin, transfer factor, and the lymphokines; (ii) agents that inhibit suppressor cell function; (iii) agents that affect the antigenic potential of tumor cells; and (iv) agents that modulate the state of differentiation of tumor cells (*18*).

Screening

In contrast to the situation for infections, experimental models for the selection of agents for clinical trial in cancer were, and continue to be, a major scientific challenge. The development of inbred mouse strains and of transplantable tumors provided a highly reproducible system for large-scale application (screening) (*6*). With the limited number of active antitumor agents available in 1955, it was demonstrated that the correlation between transplanted tumors and clinical activity was substantially better than mammalian cell and bacterial cultures, as well as selected biochemical systems (*19*). Accordingly, in the early years of the program, mouse leukemia L1210 was used as the primary screen (*20*). As more clinically active agents became available, retrospective correlations with the various preclinical evaluation systems were made, and the primary screen was modified accordingly. This became increasingly possible with advances in tumor biology in vivo and in vitro. In the 1960's and 1970's, transplanted solid tumors closely resembling the major tumors in man (lung, breast, colorectal) were developed and incorporated into the preclinical evaluation system (*2, 8*). In the past several years, human tumor xenografts in the nude mouse have been used with limited success. Also in recent years, in vitro systems for the assay of chemotherapeutic agents against a given patient's tumor (the clonogenic assay) have been developed. While this approach is still in the investigative stages, it has major importance for the selection of new agents, as well as the individualization of treatment (*21*). Such in vitro assays have profoundly influenced the successful selection of chemotherapy for infectious diseases.

The Clinical Program

Of the large number of compounds that were screened in the past 25 years, 150 were judged to be sufficiently and reproducibly active to warrant clinical trial. Of these, 40 have been found to be active in one or more categories of cancer in man (*22*).

Initial clinical (phase I) trials with a given new agent are designed to provide evidence of therapeutic effect and to determine the tolerated dose, clinical pharmacology, and qualitative toxicity of the agent. The safety and effectiveness of phase I studies has been abetted substantially by preclinical toxicology studies of proved predictive value (*23*). Phase I studies are conducted in patients with advanced cancer known to be refractory to established treatment. Such studies generally require 15 to 30 patients, and if successful are followed by phase II and III studies, which are designed to determine more precisely the presence and magnitude of antitumor activity in a spectrum of categories of human cancer (*24*).

Such studies raise the specter of human experimentation. This is particularly true of phase I studies where the physician has very limited information to impart to the patient as to the potential for therapeutic effect and toxicity. It is complicated by the fact that the patient involved has advanced cancer and may "grasp at straws." This setting has been the subject of a recent series of articles in the Washington *Post*. It is a central, complex, and poorly understood ethical issue, which deserves attention here.

A patient for whom there is no known effective treatment has two choices: no further treatment (other than supportive and symptomatic care) or experimental treatment. The emotional overlay in such a setting is major, and it is a situation rife for exploitation, as evidenced by the thriving, overpromising cancer quackery industry. The skill and empathy of the physician is sorely tested. He must know the patient and family, know how they are likely to interpret what he says, and not promote options that he knows are unacceptable. Some patients accept the inevitability of death and reject new treatment, but for many the door of hope cannot be closed. Accepting this, what on the basis of past and current phase I agents can we realistically offer the patient in terms of therapeutic effect?

As above, of the 150 agents introduced into phase I study during the past 25 years, 40 were found to have significant activity in one or more human tumors. Therefore a patient participating in a phase I trial has a 25 to 30 percent (40/150) chance of receiving an active drug. All of the 40 active antitumor agents exhibited some antitumor effects in a variable proportion of patients in a phase I trial. Antitumor effect means substantial tumor regression and symptomatic improvement lasting for one or more months. There is reason to believe, on the basis of advances in biochemical pharmacology and tumor biology, that a greater proportion of modern agents tested will be found to be effective. Immediately promising in this regard are tissue culture systems for the in vitro assay of chemotherapeutic agents against a patient's tumor (*21*).

It is inappropriate to suggest that a new agent has a chance of being curative in a phase I trial. However, patients who cannot accept that answer will generally not ask the question. Another kind of phase I study involves the novel use of established agents, such as combination chemotherapy. In such phase I studies, cure was achieved in Hodgkin's disease and testicular cancer (*25, 26*). Phase I studies may help future patients, but it is inappropriate, in my judgment, for the physician to mention this unless such information is requested by the patient. The patient may choose to discontinue participation in the study at any time.

The patient and family can be assured that the effectiveness and toxicity of the drug in vitro and in animals and the intended method of administration (protocol) has been extensively reviewed, both by an Institutional Review Board associated with the patient's hospital and by external review bodies such as those organized by the Food and Drug Administration and NCI. An Institutional Review Board includes lay persons as well as scientists not directly involved in the research under review (*27*).

Cancer is a malignant disease and requires vigorous treatment. Surgery and radiotherapy, as well as chemotherapy, are "toxic." The toxic potential of the agent, based on preclinical, and usually very preliminary clinical, studies, must

be explained to the patient and included in detail in a written consent form. For most patients, some toxicity occurs, which lasts for a few days and is completely reversible. Patients with advanced cancer have a variable symptom complex, which worsens gradually or episodically, and may be falsely attributed to the drug and sometimes cannot be distinguished, even by the skillful physician, from drug toxicity. A review of phase I studies conducted at major cancer centers indicates that 1 to 3 percent of such patients will die with (but not necessarily of) toxicity.

Unfortunately, tumor regression does not occur in most patients participating in phase I studies. In the end, the major contributions that the physician, nurses, and paramedical personnel have made in such clinical situations are optimal supportive and symptomatic care and, very particularly, the knowledge on the part of the patient and family that their physician is not only an expert in cancer care but cares for the patient. While patients and their families are grateful for whatever success is achieved in this setting, those of us involved in cancer therapeutic research can attest that immediately, and often for long periods after the patient's demise, families remember in a positive way the hope, attention, and care that was provided.

In summary, phase I studies over the past 25 years have provided limited but realistic hope to patients and families, particularly where the other choice is unacceptable. Moreover, we can hope that rapid developments in the science of therapeutic research in cancer will lead to the development of agents that are more specific for tumors; that is, that will provide a greater therapeutic effect at a lesser cost in toxicity.

Curative Cancer Chemotherapy

To date, phase I studies have provided some 40 chemotherapeutic agents that have differing mechanisms of action and that exhibit antitumor activity in one or more forms of human cancer (*22*). These therapeutic "tools" provided the opportunity for a major research effort in the therapy of clinical cancer; this research effort was largely integrated and supported by the National Cancer Chemotherapy Program.

Beginning in the latter part of the 1950's, related scientific disciplines were applied to the cancer clinical trials setting. The initial focus was on the hematologic malignancies, that is, the leukemias and lymphomas, since at that time clinically active chemotherapeutic agents were largely limited to those diseases. The natural history of the various forms of clinical cancer was studied, because such information is essential to the proper design, conduct, and evaluation of treatment programs. Quantitative criteria for assessing the disease and response to treatment were developed, and the randomized comparative trial was adapted to the cancer setting (*28*).

The sciences of pharmacology and cytokinetics, developed in animal models, provided a major rationale for clinical chemotherapeutic strategy (*29*). The major initial experiments focused on acute lymphocytic leukemia in children, and in a series of clinical trials, the principles and practice of combination chemotherapy were developed. The rationale for combination chemotherapy includes the heterogeneity of tumor cells; the problem of drug resistance; and the selection of agents with additive or synergistic antitumor effect and subadditive host effects (*30–32*). The importance of combination chemotherapy can be appreciated when it is realized that essentially all highly effective and curative cancer chemotherapy involves combinations of effective agents.

Once complete remission was achieved in a high proportion of children with acute lymphocytic leukemia, it was recognized that treatment during remission with chemotherapy was essential and that this must involve chemotherapeutic agents different from those used to induce remission. As a result, the duration of remission progressively increased, only to be accompanied by the progressive increase in the development of meningeal leukemia. Systemic drug administration was capable of controlling systemic disease, but since the drugs were largely excluded from the central nervous system (a pharmacologic sanctuary), microscopic involvement of the meninges progressed to overt leukemia. This resulted in the application of intrathecal therapy with methotrexate and brain irradiation (*33*). Such therapy proved highly effective and reduced the incidence of meningeal leukemia from over 50 percent to approximately 10 percent.

Thus, highly effective, complete remission-producing chemotherapy, followed by central nervous system "prophylaxis" and by combination chemotherapy designed to eradicate systemic microscopic disease, has resulted in a cure rate of 50 to 60 percent in children with acute leukemia. This achievement occurred primarily in the early 1960's, and some of the principles and therapeutic strategies derived from these studies, particularly those relating to combination chemotherapy and cytokinetics, were applied to patients with advanced Hodgkin's disease and non-Hodgkin's lymphoma, where cures were also achieved (*25, 34*). The development of additional agents during the past 10 to 15 years, including, in particular, bleomycin, cisplatin, and adriamycin, has, with the application of some of the aforementioned principles, resulted in the cure of 70 to 80 percent of patients with disseminated testicular cancer (*35*).

Experimental studies clearly indicate that curative treatment with chemotherapy correlates inversely with tumor burden (*36*). Thus a given chemotherapeutic agent which was marginally active against advanced gross tumor in the mouse was frequently curative against the same tumor in its early microscopic phase (*37, 38*). It was similarly recognized that a major adverse prognostic factor for chemotherapy for most human tumors was gross disease. There are many "solid" tumors where treatment of the primary tumor with surgery, radiotherapy, or both is highly effective, but relapse occurs because of the presence of clinically undetectable disseminated disease. For example, in patients with breast cancer, where the tumor is limited to the breast (stage 1), the cure rate with local treatment only (surgery, radiotherapy, or both) is in the range of 80 percent. However, if the tumor has spread to the axillary lymph nodes, surgery and radiotherapy will provide local control, but relapse at distant sites will occur in 70 to 80 percent of patients because of disseminated disease. "Adjuvant" chemotherapy is given immediately after treatment of the primary site in those patients at high risk of having disseminated disease. This strategy was used initially, and successfully, in the early 1950's for children with Wilms' tumor (*39*), and was subsequently shown to be effective in increasing the cure rate in several relatively rare solid tumors in children.

In the past 10 years, this adjuvant treatment strategy has been the subject of a number of clinical trials (*40, 41*). In general, that chemotherapy which is most effective against advanced states of a given tumor has been used in the adjuvant setting. Since cancer is a chronic disease, and since adjuvant treatment is evaluated primarily on the basis of time to relapse, it may take a long time to evaluate the effectiveness of an adjuvant study. Breast cancer, the most common cause of death from cancer in women, is important and instructive in this regard.

Controlled studies of adjuvant chemotherapy of breast cancer were initiated in 1972. These studies involved initial control of the primary tumor with surgery. Patients with axillary metastases, that is, at high risk of dissemination, were randomly allocated to treatment with chemotherapy or to no treatment. Essentially all studies, particularly those involving combination chemotherapy, have led to a significant decrease in the relapse or failure rate as a result of chemotherapy, particularly in premenopausal women with one to three positive nodes. Although the results of these studies are positive, their full impact must await further follow-up, in view of the chronicity of the disease (*42*).

In summary, chemotherapy alone, or in the multimodality (adjuvant) setting, is curative for patients with acute lymphocytic leukemia, Hodgkin's disease, diffuse histiocytic lymphoma, testicular cancer, gestational choriocarcinoma, Wilms' tumor, Ewing's tumor, embryonal rhabdomyosarcoma, and Burkitt's lymphoma. In addition, chemotherapy is probably curative (pending further follow-up) for limited small-cell lung cancer; acute myelogenous leukemia; and, in the adjuvant setting, for breast cancer and osteogenic sarcoma.

Curative Cancer Chemotherapy and U.S. Cancer Mortality

A major indicator of curative treatment is the impact on national cancer mortality statistics. The Cancer Surveillance Epidemiology and End Results (SEER) program at NCI has monitored both the incidence and mortality of all of the major forms of human cancer. The National Cancer Act of 1971 promoted and supported the training of a large number of clinical oncologists. This made possible the application of sophisticated cancer evaluation and treatment programs to the population at large. In general, for the 13 diseases mentioned above, there has been a significant reduction in national mortality statistics, and the magnitude of the reduction for a particular disease correlates with the know effectiveness of treatment for that disease as well as the year such treatment was introduced and became widely used (*43, 44*). Specifically, the decline in mortality in the United States between 1966 and 1976 for the following diseases has been: Wilms' tumor, 66 percent; Hodgkin's disease, 39 percent; pediatric leukemia, 38 percent; non-Hodgkin's lymphoma, 24 percent; bone tumors in children, 23 percent; premenopausal breast cancer, 19 percent; and for testicular cancer, between 1973 and 1978, 34 percent. Whereas the number of patients cured annually by chemotherapy was less than 10,000 per year in the United States 10 years ago, it is now greater than 40,000. Chemotherapy tends to be more effective and have a greater potential for cure in the younger individual. Thus, when cancer mortality over the past 15 years was analyzed by age groups, it was found that there has been a 20 to 43 percent reduction in cancer mortality in the United States in subjects under the age of 45 (Fig. 1) (*44*). Detailed analyses of cancer incident and stage at time of diagnosis over these time periods indicate that the decline is a result of improved treatment, largely improved chemotherapy. This decline is countered by an increase in cancer mortality in older subjects, almost all of which is due to smoking-related cancer, particularly lung cancer (Fig. 1). Indeed, when smoking-related cancers are subtracted, there has been a slight decline in the incidence of cancer in the United States over the past 35 years (*45*).

In addition, chemotherapy short of cure can produce substantial tumor regression and symptomatic improvement lasting a number of months in patients with metastatic breast cancer, cervical cancer, head and neck squamous cell carcinoma, insulinomas, ovarian cancer, soft tissue sarcoma, chronic leukemias, and nodular lymphomas. It remains true, however, that chemotherapy has been of limited benefit for some of the major forms of cancer, such as non–small-cell lung cancer, melanoma, and gastrointestinal and prostate cancer.

Toxicity

These therapeutic results attest to the efficacy of cancer chemotherapeutic agents. However, some adverse effects on normal organs occur (toxicity). Since the dose response curve for most cancer chemotherapeutic agents is steep, it is desirable to treat at dose levels approaching the maximum safe and reasonably well tolerated dose. As predicted from cytokinetic studies, toxicity commonly relates to organs with a high rate of cell turnover. This includes the bone marrow, gastrointestinal tract, and the hair follicle. Transient suppression of the bone marrow with chemotherapy leads to a decrease in platelet and white cell counts in the blood. With major attention being given to pharmacology, bone marrow reserve, and appropriate dose adjustment, some degree of bone marrow suppression, short of infection and hemorrhage, can be achieved. Gastrointestinal ulceration toxicity is less common and also must be modified by dose adjustments. The major subjective manifestation of toxicity is nausea and vomiting, which is a significant problem with some 60 percent of the agents currently used. Chemotherapy-induced damage to the hair follicle may produce temporary loss of scalp hair. Although the above and other toxic manifestations significantly compromise the quality of life while the patient is receiving therapy, they are usually completely reversible (*46*). New approaches designed to prevent or ameliorate chemotherapy-induced toxicity, such as nausea and vomiting, are being investigated. New classes of antiemetics have been discovered (*47*), animal models for the evaluation of antiemetics have been identified, and studies of the relation between drug structure and activity are under way. Significant progress has already been achieved in reducing the incidence of chemotherapy-induced nausea and vomiting over the past several years (*48*).

In addition to the acute effects of cancer chemotherapy, long-term effects may also occur. These effects include suppression of ovarian function and spermatogenesis, and, with the anthracycline class of drugs, cardiac toxicity. A more ominous late toxic manifestation has been the development of secondary tumors, particularly acute myelogenous leukemia. Some antitumor agents, such as the alkylating agents, alter the structure of DNA, and therefore are mutagenic in bacterial assay systems and carcinogenic in experimental animals. It is not surprising, therefore, that such agents have proved to be carcinogenic in man. However, the generalization that all cancer chemotherapeutic agents are carcinogenic is not true. Many agents, such as the vinca alkaloids and the antimetabolites (which may alter the synthesis but usually not the quality of DNA) are, in general, not carcinogenic in experimental animals or in man. The dose of, and particularly the duration of treatment with, potentially carcinogenic chemotherapeutic agents correlates strongly with the subsequent development of tumors. An increase in the incidence of secondary tumors, particularly acute myelogenous leukemia, has been observed in several forms of human cancer treated with agents that are potential carcinogens (the latent period for secondary tumor development is generally

greater than 2 years). Hodgkin's disease has the highest rate of secondary acute myelogenous leukemia (*49*). Patients with certain stages of Hodgkin's disease are often treated with combination chemotherapy, which includes the potent mutagens procarbazine and nitrogen mustard, and with extensive radiotherapy, which is also potentially carcinogenic. The incidence of secondary acute myelogenous leukemia in such patients is approximately 5 percent. Although this is unsatisfactory, it must be balanced by the knowledge that 50 to 80 percent of patients with Hodgkin's disease can be cured by radiotherapy and combination chemotherapy. For several other forms of cancer treated with alkylating agents, the incidence of secondary tumors is significantly increased, but to a much lower level (*50*).

In recent years the strategy of clinical trials has included attempts to decrease the risk of carcinogenicity. Thus there is good evidence that 4 to 6 months of treatment for many tumors (testicular cancer, Hodgkin's disease, adjuvant-treated breast cancer) is sufficient and that the longer durations of treatment previously used are unnecessary. Second, there are diseases for which there are numerous active agents (for example, Hodgkin's disease), and hence it may be possible to construct curative chemotherapy regimens that exclude most or all potential carcinogens.

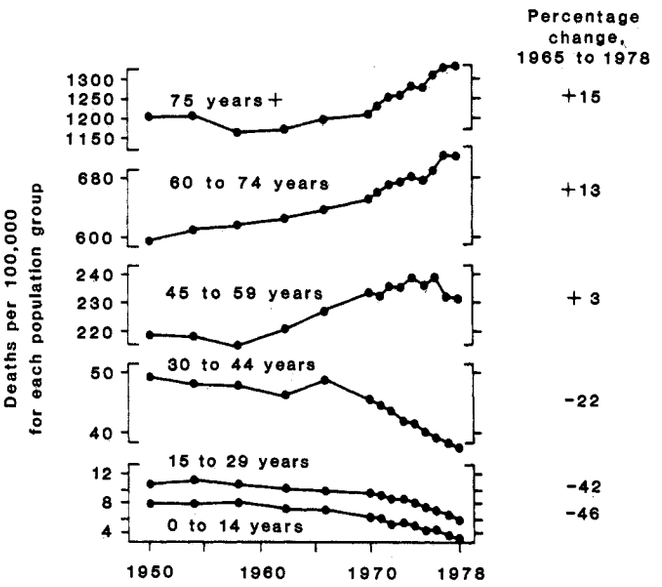

Fig. 1. Age-specific cancer mortality trends, 1950 to 1978.

The Future

Although the National Cancer Chemotherapy Program has received some criticism, it is, on the basis of any balanced analysis, at least a qualified success. Cure or palliation has been achieved in an increasing proportion of patients, and many problems and prospects previously unperceived have been brought into focus and are the subject of current research. Of particular importance is the evidence that basic and applied science is leading to the development of more effective and less toxic agents in the area of cancer chemotherapy, immunotherapy, and endocrinology. A few areas of research deserve emphasis.

Different clinical therapeutic strategies are under study. Where local control of tumor is difficult to achieve, such as in patients with head and neck cancer, chemotherapy is being used initially with the intent of achieving tumor regression and therefore improving the prospects for definitive treatment with surgery or radiotherapy (*51*). This approach has been successful in Wilms' tumor and certain other childhood tumors (*41*).

Certain chemotherapeutic agents increase the sensitivity of tumors to radiotherapy. Of these perhaps the most interesting are the nitroimidazole compounds (misonidazole). Hypoxia in areas of compromised blood supply occurs in the majority of tumors, and hypoxic cells are relatively radioresistant. Misonidazole by virtue of its electron affinity restores radiosensitivity (*52*).

Many of our current established cancer chemotherapeutic agents can be modulated pharmacologically by various metabolites. Thus the biochemical effects of the folic acid antagonists can be reversed by leucovorin, which supplies the product of the inhibited enzyme dihydrofolate reductase. With proper timing, tumor regression occurs while toxicity is prevented in some forms of cancer (*53*). There is a long precedent in cancer chemotherapy to the effect that progress can be achieved by the more imaginative and effective use of established agents.

The biochemical tools today are such that it is possible to determine at a molecular level the mechanism of action of some of our established antitumor agents and therefore the basis of whatever specificity exists against tumor cells compared to normal cells. Such knowledge has led to the more rational synthesis of congeners of established agents with the potential for greater therapeutic effect.

There are a number of growth and modulating factors in the microenvironment that regulate the proliferation and behavior of normal cells. Many of these factors may also affect tumor cells. In studies in vitro, some of these factors, such as growth factors and lymphokines, have been identified. The first such new agent to reach the clinic has been leucocyte interferon (*54*). Since many of the factors are polypeptides it should be possible to produce them by recombinant DNA technology.

Although the focus of cancer chemotherapy generally has been on the destruction of tumor cells, another approach relates to the induction of differentiation, a process that occurs in normal cells and that may be induced in tumor cells experimentally by environmental (including chemotherapeutic) interventions (*55*).

Studies of tumor immunology, particularly as a result of monoclonal antibody technology, are providing new knowledge about the pathogenesis, diagnosis, and treatment of cancer. On the basis of the antigenic determinants of various classes of lymphocytes, new rational classifications have been developed for acute lymphocytic leukemias and non-Hodgkin's lymphomas have emerged that have prognostic and chemotherapeutic correlates. A patient's immune response may be selectively altered by cancer and can be selectively manipulated by such antibodies. Monoclonal antibodies alone or complexed with highly cytotoxic chemotherapeutic agents (immunotoxins) are in early, phase I, clinical trials (*56–58*).

Finally, advances in tumor biology should provide an increasing number of future biochemical "targets" for treatment. One, or many, examples is the approach to the identification of the transforming gene and its products in human tumors (*59*).

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The Role of Science in a New Era of Competition

George A. Keyworth, II

Anxiety runs high in Washington when there is a change in administration, and the delay in my arrival as science advisor no doubt contributed to the uncertainty last year about the role of science and technology in the Reagan Administration. The first formal presentation of the new Administration's science policy was made in June 1981 at the sixth annual AAAS Colloquium on R & D and Public Policy. That presentation of the broad context for science and technology policy was an event that I enjoyed thoroughly—until I started reading in the press what it was I had supposedly said and what it supposedly meant. Now, a year later and a bit wiser, we owe it to ourselves to look realistically at the situation and opportunities at hand.

I would like to look beyond the immediate topic of the research and development budget for fiscal year 1983. Instead, I want to offer some thoughts about how science and technology fit into this Administration's goals for the country and share some ideas on what role we, the science community, must play in coming years.

No conference on federal R & D priorities can ignore the overriding significance of our country's economic condition. It is the dominant factor in virtually all deliberations on policy issues at the White House. Not only does the economy determine how much R & D the nation can pay for, but it also influences what kind of R & D we will do. As I will discuss, R & D are important to our immediate economic recovery and critical to our long-term health—and the President is well aware of that.

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Controlling Federal Spending

The President has been attacking the nation's economic problems directly through a combination of fiscal policies. In spite of all the public hand-wringing, I am convinced that most people recognize the inescapable truth of what must be done to restore America's luster. And in June the Congress made some hard political choices and finally approved a responsible federal budget for fiscal year 1983.

It is clear that economically this has not been a good year for the United States. For nearly two decades we have been living increasingly beyond our means—or neglecting to replenish our means to keep pace with our aspirations—and it is finally taking a brutal toll. High inflation, higher taxes, and crippling interest rates have been eroding our ability and incentive to prepare for the future.

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