The Basis for Progress in Chemotherapy

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In the not too distant past, a paper on cancer chemotherapy would have been read only by a few of the author's most loyal friends. Obviously, a new day is here. Chemotherapy has effected profound changes in the outlook for patients with disseminated cancer and physicians everywhere are eager to make chemotherapeutic treatments available to their patients. This paper will attempt to outline the basis for progress in cancer chemotherapy—its present status, past history and future directions.

Present Status

Chemotherapy is now the key factor responsible for long-term survival in at least 10 types of widespread cancer, occurring largely in children, adolescents and young adults. (Table 1.) In other types of cancer such as the solid tumors, especially carcinomas, usually found in patients in middle and older age groups, chemotherapy has caused an increase in the number of complete remissions and a lengthening of the duration of these remissions, although long-term survival has not yet been demonstrated. In sarcomas, recent clinical developments suggest that chemotherapy may produce complete remissions in the future.

Does long-term survival mean the patient is "cured"? Since the word "cure" is emotionally charged and has

Table 1. Diseases Highly Responsive to Chemotherapy
Burkitt's Lymphoma
Choriocarcinoma
Acute Lymphocytic Leukemia
Hodgkin's Disease
Lymphosarcoma
Mycosis fungoides
Embryonal Testicular Cancer
Wilms' tumor
Ewing's sarcoma
Rhabdomyosarcoma
Retinoblastoma

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many shades of meaning, I prefer to use the term normal life expectancy. Thus, long-term survival is achieved when cancer patients after treatment die no faster than the cohort of the same age and sex in the general population.

Normal life expectancy has been produced in varying proportions of patients with at least the 10 types of cancer listed in Table 1; these patients are usually children, adolescents or young adults in whom few, if any, deaths would normally be expected. In all cases, normal life expectancy was negligible prior to the advent of chemotherapy, or far below the life expectancy now possible. The percentage of patients achieving normal life expectancy range from about 90 percent in those with Wilms' tumor to about 15 percent in patients with metastatic testicular cancer. These survival results are largely due to combined treatment with chemotherapy and surgery or radiation therapy; chemotherapy is used as a single modality of treatment only in patients with choriocarcinoma and Burkitt's lymphoma. However, in each instance, chemotherapy is the *vital* factor in bringing about normal life expectancy.

How is progress judged in those cancers where chemical control has caused a marked effect but where there has been insufficient observation time to reach conclusions on normal life expectancy? Two therapeutic milestones invariably preceded the demonstration of improved survival in the 10 diseases listed in Table 1. These were: (1) an increase in complete remissions of widespread disease induced by chemotherapy; (2) the lengthening of the induced remissions. In a number of the more common solid tumors of middle and older age groups, chemotherapy is producing an increasing percentage of complete remissions of significant duration which, from past experiences, should lead to increased life expectancy once sufficient time has elapsed to make observations.[1]

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Recent clinical evidence suggests that these milestones on the road to normal life expectancy may soon be exhibited in cancers as yet less responsive to chemotherapy, such as the sarcomas.

Past History

Extensive advances in the control of some cancers by means of chemotherapy have occurred in roughly a decade. How did chemotherapy achieve so much in so little time? The answer is significant not as historical window-dressing but so that the mechanisms and apparatus responsible for present success can be understood and exploited for the vigorous pursuit of the 90 cancers still to be controlled.

Between 1945-1955 several chemotherapeutic agents were discovered by pioneers such as Drs. Sidney Farber, Cornelius Rhoads, Alfred Gilman, Joseph Burchenal and others, working with the research teams of pharmaceutical houses.[2] Industry soon found that research and development for antitumor drugs were far too costly and in 1955 Congress supplied the resources and authority for such a program at the National Cancer Institute. This program was intended as a long-term, systematic effort to establish an apparatus for the development of anticancer drugs.

Before such an apparatus could be produced, three things were required: a scientific team; selection and calibration of all the systems (including screening, toxicology, pharmacology, formulation and chemical production) required for

drug development; and a valid, safe way of carrying out clinical trials. From 1955-1965, the team was forged, drug development systems devised and calibrated, and a national clinical trials network perfected. The scientific team is national in character and includes scientists and physicians in universities, research institutes, federal government laboratories and hospitals and the pharmaceutical and chemical industries.

When the program started in 1955, innumerable suggestions were presented regarding screening systems for antitumor activity, systems for predicting toxicity in man, for pharmacologic studies, and many other areas. A few systems had to be chosen from this morass. Not until 1965 did the members of the team prove that specific preclinical systems were valid in predicting drug effects for patients.[3] These correlations were possible only after the national clinical trials network, largely carried out by the cooperative groups, had shown how drugs could be studied quantitatively in a variety of clinical cancers.

Both preclinical and clinical systems of drug development are extremely useful, but far from perfect. They have many shortcomings, which are well known; intensive research is being conducted to develop better systems, and as improvements are discovered, they are introduced into programs of screening, toxicology and pharmacology and the clinical trials. Drug development for cancer is a dynamic affair that permits progressively refined focusing on how to predict efficacy and safety for patients.[4]

The largest addition to the chemotherapeutic drug armamentarium has come since 1965, but not all of these agents have come solely from the national program. Because the team maintains a worldwide surveillance, new leads from abroad are examined in carefully calibrated systems and, if criteria for activity are met, are brought rapidly into clinical trial in the United States.

Future Directions

Where is chemotherapy going? One immediate answer is the use of combination chemotherapy and chemotherapy combined with other therapeutic modalities.[5] Perhaps the most promising avenue of investigation will be combinations of drugs administered after surgical excision of the primary tumor. To date, most surgical adjuvant studies have not exploited modern principles of chemotherapy.

Other future directions of chemotherapy depend largely on the solution of several key problems.[6] (Table 2.)

Cell Population Kinetics

It is apparent that some cancers are highly susceptible to drugs and others are not. Highly responsive tumors double their size in a few days, the intermediate responders in weeks and nonresponders in months. A great deal of research has been focused on this apparent correlation between rates of doubling and drug susceptibility and it has been shown that drug susceptibility of tumors is related to the size of the growth fraction. The growth fraction of a tumor is the percentage of cells progressively moving through the mitotic cycle at any one point in time. Differences in growth rate of tumors defy any simplistic, general statement, but a major determinant of growth rate is the size of the growth

Table 2. Key Scientific Problems

Cell population kinetics
Pharmacokinetics
Assay of tumor cells
Supportive care for infections
Role of immunotherapy
Biochemical screening

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fraction.[7] Thus, a tumor with 95 percent of its cells dividing will grow at a much faster rate than one with five percent of cells dividing. The implication of a larger growth fraction is that the cells in the active proliferative state are committed to go through DNA synthesis (S-phase). Because most active antitumor drugs have their major killing effect during DNA synthesis, one can explain the drug susceptibility of the large growth fraction tumors and the nonresponsiveness of the small growth fraction tumors. A tumor with 95 percent of its cells going through DNA synthesis will be seriously damaged by inhibitors of DNA synthesis, while a tumor with five percent of its cells going through S-phase will not be affected.

As with most generalizations, the actual reality is exceedingly complex and there is a great deal to be done to understand the interrelations in each tumor type. Nevertheless, this general theorem of tumor biology has provided the beginnings of understanding successes and failures of cancer chemotherapy.

Pharmacokinetics

Research continues to search not only for more effective, less toxic drugs, but also for the best ways to use existing drugs.[8] This research comes under the heading of pharmacokinetics: the study of the circumstances under which a drug will kill large numbers of tumor cells without harming too many normal cells. Just as tumor cells have widely varying growth fractions, so do normal cells. Normal cells, such as bone marrow, that have large growth fractions, suffer most markedly from antitumor drugs. By studying the drug concentrations maintained for varying time periods at different cell sites, it is possible to calculate dosage schedules that will give the greatest tumor cell kill with the least toxicity to normal cells. This information can be translated into dosage regimens that will most benefit the patient. With arabinosylcytosine (Ara-C), for example, it was possible to show in a mouse leukemia that certain dosage schedules were completely ineffective, while other dosage schedules were curative. This resulted in important improvements in the way Ara-C was used in patients. Pharmacokinetic studies of this sort are being extended to most of the known active agents. While there is still much to be done, it is clear that the effectiveness of anticancer drugs is greatly influenced by changes in dosage schedule. This is probably because of the necessity of arranging the dose schedule in a way appropriate to cell population kinetics of the tumor. In any event, pharmacology and cell population kinetics cannot be studied as isolated disciplines but must be looked at concurrently. Application of this combined approach to all 40 chemotherapeutic drugs now available for many tumor types is the long-term goal, but as a few general principles emerge, the rate of understanding should accelerate.

Assay of Tumor Cells

More accurate means of measuring how much of the tumor has been killed by chemotherapy are also being studied. Generally, when clinical cancer is diagnosed there are 1×10^{12} tumor cells in the body. If treatment reduces the number to 1×10^{9} cells, the tumor is usually too small to detect, and there is an apparent complete remission, although a billion tumor cells remain. How long and how intensively should therapy be carried out after clinical remission? In acute lymphocytic leukemia, therapy is continued for long periods of time—perhaps two

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years, after the patient reaches complete remission. Is this too much therapy to kill the last billion cells or, in some patients, is it too little? The solution is suggested in quantitative assays which can now titrate treatment in patients with choriocarcinoma by measuring the amount of gonadotropin—a chemical by-product of the tumor—in the urine to see if all the tumor cells have been killed. This, of course, would be the ideal for every cancer patient, not only for monitoring the efficacy of chemotherapy but also for judging the completeness of any type of therapy and when it is safe to discontinue treatment. The discovery of tumor products, including immunologic materials—tumor antigens—that could be used quantitatively to titrate extent and duration of therapy would do more to speed up the chemical control of cancer than any other single technique.

Systems to Predict Drug Effects

Most of the drugs now used in human cancer have come from empiric screening in mouse tumors. The classical mouse tumors were all fast growing, large growth fraction tumors. A search was made for mouse tumors with small growth fractions and several have been found that mimic the situation seen in patients with lung or breast cancer. This second generation screen is now used to select drugs for trial in patients with small growth fraction tumors.[9] A third generation screen of "spontaneous" virus induced tumors such as AKR leukemia and C_3H mammary cancer is under study. These might be useful as models to study the effect of antiviral compounds, inhibitors of reverse transcriptase, and immunotherapy in selecting drugs aimed at preventing late relapses. A fourth generation screen will be possible in the future, when some of the current biochemical research indicates in vitro the way to interfere with specific molecular steps in the production of DNA by tumors.

Also of great importance to the success of chemotherapy are investigations on the role of immunotherapy and supportive care of the patient. Research on cancer chemotherapy must always include concurrent assessment and exploitation of these host factors.

Conclusions

In the first 10 years of cancer chemotherapy, a few drugs were developed that could temporarily halt the progression of fatal cancer. In the next 10 years, the nation's scientists and physicians learned how to search for better drugs in a systematic way and how to use these drugs to rid the patient of all tumor cells. In the last seven years or so, we have begun to see the attainment of normal life spans in patients with certain rapidly growing tumors. These results have been so striking that the American Cancer Society and the National Cancer Institute are joining forces in a control program to ensure the rapid extension of modern chemotherapy and a new subspecialty has been established by the American Board of Internal Medicine. These last years have also seen the beginning of drug control of the slowly growing tumors and a dawning of understanding of why they are biologically different from their drug-responsive cousins. The biggest challenge is, of course, the chemotherapeutic control of common cancers and I believe we have some, but not yet all, of the research tools necessary to increase life span.

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Cancer Chemotherapy Is Many Things

. . . Cancer chemotherapy is many things. It is not just "screening" as some seem to think, nor is it just organic chemistry, biochemistry, cell population kinetics, pharmacology, or sophisticated experimental therapeutics in model systems and in man. It is all of these things and many more, but most of all it is discovery, development, collation across disciplines, and application to man with (for good reason) a prevailing sense of urgency. We want and need and seek better guidance and are gaining it, but we cannot afford to sit and wait for the promise of tomorrow so long as stepwise progress can be made with tools at hand today.—Howard E. Skipper, Ph.D: Cancer Chemotherapy is Many Things: G. H. A. Clowes Memorial Lecture. Cancer Research. 31: 1173-1180, 1971. P. 1178.