Advances in
CANCER RESEARCH

ADVANCES IN CANCER RESEARCH

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Advances in Chemotherapy of Cancer in Man

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I. Introduction

A consideration of the status of chemotherapy of cancer in man is based today upon actual achievement of objective effects against several forms of disseminated cancer by the action of chemical substances. There is still no chemical compound which alone is capable of producing a cure of cancer in man. The advances of the past ten years have come both from the pioneer endeavors and carefully planned programs in a few institutions in the world and from critically conducted empirical programs of clinical investigation. That the break-through demonstrated by the successful, albeit temporary, therapeutic effects of a small number of chemical compounds against a few of the many forms of cancer in man was made possible largely because of empirical approaches, need in no way diminish the magnitude of the accomplishment nor discourage the investigator who seeks always for a rational approach in research. For it is clear that the advances of importance in the past ten years in the chemotherapy of cancer of man, while empirically produced, have not been the product of brilliant guesswork or luck. They have occurred as part of carefully planned efforts in a small number of institutions whose purpose it was to find therapeutic weapons against cancer. Such laboratories and clinics have made use of the vast amount of useful knowledge available in disciplines far removed from the field of chemotherapy of cancer. They have had also to fashion new techniques and vocabulary in initiating a new era in cancer research. Their efforts and initial success have stimulated hope of similar attacks on other problems in medicine once regarded as hopeless, such as certain neuropsychiatric states.

II. Clinical Considerations

1. The Problems of Clinical Investigation in Cancer Chemotherapy

The evaluation of a chemical compound for anticancer effect must be based upon sound knowledge of the life history and biologic behavior of the many forms of cancer, the precise definition of criteria used in formulating conclusions concerning response or efficacy of treatment, and finally, the creation of an experimental design capable of meeting the standards of scientific research set up in the wards and clinics of the hospital where, by the very nature of the environment, research standards dare not be the primary consideration. The word *cancer* is used as a covering term under which are grouped many probably unrelated diseases characterized by natural histories and biologic behavior so different from one another as to make the word cancer meaningless except for its historic connotation. Conclusions concerning the effect of a given treatment on any form of cancer may not be carried over to other tumors. It is likewise impossible to conclude from the failure of response of one or more forms of cancer that a given agent will be of no value against other tumors.

In the past, clinical evaluation of cancer chemotherapy has been conducted on patients either with cancer disseminated from the very outset, such as leukemia, or with advanced cancer beyond the therapeutic reach of surgical or radiological techniques. The time will come when chemical agents may be employed with propriety much earlier in the course of the disease, when greater familiarity with the possibilities of chemotherapy is available to the clinician. Beginnings of this kind have already been made against such tumors as the Wilms' tumor, since sufficient experience is at hand with surgical and radiological techniques to permit a statistical conclusion, after a period of years, of the value of adding a carcinolytic agent at the time of surgical intervention and irradiation. Each kind of tumor must be examined on its own merits. The time has not yet come for widespread "prophylactic" use of any carcinolytic agent presently available.

Variables within one category of cancer, such as carcinoma of the lung or of the large intestine, of sufficient importance to create serious difficulties in the selection of comparable series of patients must be considered. These include the age and sex, the state of nutrition and of the bone marrow, the presence of sensitivity to drugs or to foreign proteins, or of unrelated diseases such as hypertension or chronic nephritis, the distribution, size, and exact anatomic location of metastases which alone may account for physiologic disturbances not necessarily a part of the clinical

course of any one form of cancer. Mention should be made, too, of the importance of economic, family, and social problems which may have direct bearing upon the conduct of the clinical investigation. The character and duration of previous treatment and possible toxic effects of such treatment upon organs uninvolved by the tumor itself may alter the response to a subsequently administered chemical agent. The magnitude of the problem is increased by an assumption which should form the basis of all experimental clinical chemotherapy: no treatment should be given to a patient that is not designed primarily for the good of the patient. A corollary is that the patient may not be deprived of treatment of proved value merely to permit the trial of a new agent. It is impossible to assign patients to a group of "untreated controls" as is customary in animal experimentation. Finally, the clinical investigator must be prepared to terminate or alter any course of treatment if the continued survival or comfort of the patient requires the addition of other forms of therapy, because clinical investigation in the field of cancer may be carried out only as part of the *total care* of the patient.

It is understandable, therefore, that "experimental design" looks much more attractive on paper than in the actual execution of such a program when applied to man. Within the limits imposed by these restrictions clinical investigation of importance, nevertheless, can be planned, and important progress can be made. Two somewhat different forms of clinical investigation in cancer chemotherapy may be defined. The first concerns the primary explorative phase of research with a new chemical compound which has been studied previously with great care for toxicity, microbiological, and anticancer properties in laboratory systems and, ideally, for leads concerning mechanism of action, distribution, fate, metabolism, and excretion. In carefully selected patients who have failed to respond to all other forms of therapy, such new material may be administered with caution for the determination of the effective dose level and for observation of possible carcinolytic and carcinostatic properties. The new agents should be tried in such studies against as many different kinds of cancer in man, and in as many different situations within any one form of cancer as possible before a conclusion is reached concerning its probable value.

A second type of clinical investigation is of value when leads concerning carcinolytic activity of a compound are uncovered by the first kind of study. Now, the special virtues of uniform conditions, carefully defined criteria for selection of patients, and administration of a compound under identical conditions, and from the same batch, are required. In this plan a number of institutions may band together and pool their resources for the detailed study and evaluation of a carcinolytic agent under as

ideal conditions as possible. With full appreciation for the difficulties and restrictions of clinical investigation in clinical cancer chemotherapy, adequate data eventually should be forthcoming from such combined cooperative ventures. Those responses to the action of a chemical agent selected for evaluation should be studied under conditions which permit maximum objectivity. Tumor masses should be measured with the aid of a caliper, visible masses should be photographed, and all data obtainable from hematologic and radiologic procedures should be recorded. Histological proof of the exact nature of the tumor is required. In short, the standards of clinical investigation in cancer chemotherapy are no different from those in any other form of clinical investigation, nor should they differ from the routine expert study and care of any patient with a problem in any well-conducted clinical institution. A thorough history will include special consideration of environmental factors in a search for exposure to carcinogenic substances, attention to ingestion of chemicals or drugs, or antibiotics, and detailed recording of family histories as far back as possible to provide data for genetic research. A complete initial study will include hematological and bone marrow studies in more detail than is ordinarily the case because of the effect on the hematopoietic system of most carcinolytic agents. Documentation by photography, and x-ray examination as indicated, but usually at frequent intervals, is of permanent value. Other laboratory determinations on the blood, excreta, or body fluids, liver or kidney function tests, uric acid or certain enzyme studies form a part of intelligent experimental design and thorough study of the patient. There is unfortunately no single routinely performed laboratory procedure which alone will permit the evaluation of the response of the patient and his tumor to the action of a chemotherapeutic agent. The final evaluation must be based upon the effect on and, hopefully, the disappearance, of the primary tumor or the metastases, truly striking improvement in the health of the patient (not merely an increase in well-being) and prolongation of life, which in itself represents a conclusion requiring careful qualification and large experience.

It is clear that unless a carcinolytic agent acts rapidly and strikingly in repeatedly bringing about the destruction and disappearance of tumor masses, evaluation is beset by many difficulties.

2. Emotional Problems Associated with Clinical Cancer Chemotherapy

Emotional problems of importance associated with clinical cancer chemotherapy are encountered on the part of the patient, the family, the doctors, nurses, and other hospital workers associated with the patients, the scientists and doctors in other institutions, the medical profession as a whole, and the public awaiting progress in cancer research. Experi-

ence with the study of the action of chemical compounds as part of the total care of 1700 patients with disseminated or advanced cancer during the past 10 years has demonstrated the importance of adequate preparation both in personnel and in facilities for the handling of emotional problems of the patient and the family. For them the greatest mental peace is obtained by the realization that a devoted doctor or a group of doctors, nurses, and hospital workers are doing everything that can be done in the light of available knowledge for the comfort, treatment, and happiness of the patient. The patient's needs are met by his realization that he will never be abandoned. The needs of the family are met if a policy of complete truth is adopted and if the only promise that is made by the doctors is based upon the hope that the next forward step may come in time, from any one of the many institutions where research is going on, for the benefit of the patient whose life is being prolonged by the best forms of therapy available today. If the quarters in which the patients are cared for are bright and cheerful, and if the entire atmosphere is one of guarded optimism based upon actual achievement in laboratory research, fear is more easily dispelled and replaced by courageous handling of problems.

The feeling of pressure on the part of those in laboratory aspects of research may be great indeed if such scientists are exposed to the clinical problem of the patient who is dying because of the failure of more rapid progress in cancer therapy. Such emotional disturbances are not entirely unfortunate. The problem of the patient is a pressing one, and research dare not remain unnecessarily long in the ivory tower. The emotional disturbances of other doctors carrying out research in chemotherapy of cancer can be relieved by cooperative, voluntary programs which permit constant exchange of information and of progress. The medical profession, too, is in constant turmoil because of premature overenthusiastic reports concerning the great advances in the therapy of advanced cancer. The establishment of better means of communication of the results of research to the medical profession by techniques other than those of the medical journals will do much to protect the emotional equilibrium of men who carry the burden of daily contact with patients all over the world.

It is the general public which requires more consideration of its emotional disturbances concerning cancer. This is best accomplished by frank discussions of the progress of research from official, reliable, and impersonal sources. When such an agency is set up to replace the frequently inaccurate and sometimes lurid accounts of cancer research progress, the emotional state of the public which fears cancer, and sincerely desires the end of this threat to comfort, life, and security, will swing toward the normal. We are dealing with a problem of universal

concern which can be handled only by accurate and authoritative communication.

III. The Chemotherapy of Acute Leukemia

1. General Considerations and Definitions

The chemotherapy of acute leukemia provides a suitable example of advances in the treatment of one of the few forms of disseminated cancer in man which has responded to chemical agents. Before 1947 every attempt at influencing the predictable course leading invariably to death of a patient with acute leukemia failed (Watkins, 1947). Only the occurrence of the poorly understood brief "spontaneous remission" (Diamond and Luhby, 1951; Tivey, 1954) which was found in from 1% to 10% of all patients with this disease held out any hope of prolonging survival by a few weeks of nearly normal life.

In 1947 and 1948 investigations on the action of folic acid conjugates and later folic acid antagonists (Farber, 1948; Farber *et al.*, 1948) resulted in the first planned induction of remissions with Aminopterin in children with acute leukemia. Aminopterin proved to be a potent agent. From the exploration of its usefulness and the clinical trials with 4-amino PGA analogues several aspects of the limitations of antileukemic chemotherapy emerged. One was the development of "resistance" in patients who for a time had responded well to the antileukemic agent and another the concept of "cross resistance." This term indicated that a tumor which had responded to, and later become resistant to the chemotherapeutic agent—aminopterin, for example—would not respond to any other folic acid antagonist analogue. Both concepts, first formulated clinically, have been proven in the laboratory (Burchenal *et al.*, 1950b; Law and Boyle, 1950) and have also been found to hold true for other antitumor agents, notably the purine antagonists, 6-mercaptopurine and thioguanine.

Another early observation (Farber, 1948) directed attention to the potential toxicity of antileukemic antimetabolites. So far every chemical agent effective against the disease has also possessed the capacity of producing some measure of damage to the normal hematopoietic system and the mucosal membranes of the host when administered in toxic amounts. The ability to produce such toxicity does not, however, confer antileukemic properties upon an agent.

Such observations led some investigators to the unfortunate practice of inducing severe toxicity with a given agent to make certain that the patient had received sufficient therapy to induce a remission (Dameshek, 1949). This method proved unduly dangerous for the patient and was not necessary for the production of clinical improvement. By careful choice

of the dose for each patient, remissions could be produced without any attendant toxicity (Farber, 1952, cf. Toch, pp. 149–151).

It became clear quickly that any attempt at evaluating possible results of the chemotherapy of acute leukemia would require a strict set of criteria. Any such criteria would have to make allowances for several possibilities. The following is an outline of the criteria used for several years to good advantage:

Complete remissions are defined as a complete disappearance of clinical and hematological evidences of disease and the presence of no more than 7% blast cells in the marrow. These remissions must be further defined as having been caused by the chemotherapy or as "spontaneous" in nature, associated with a significant infection.

Partial remissions are defined in terms of clinical improvement to the usual activity normal for age and sex, with peripheral blood findings approximating the normal; the bone marrow contains no more than 30% blasts. Again attention must be given to the probable cause of the improvement.

Some patients obtain marked *clinical improvement* without significant hematological changes. Allowances should be made for patients who received therapy too briefly, usually less than 21 days, to have had a fair clinical trial, and for patients whose records can not be evaluated for various reasons. *Failures* must be specified as such. Usually for critical evaluation of any agent the total group of patients should be divided into these groups and percentages may then be calculated for the total group. Only the complete remissions and partial remissions that were not associated with severe infections in the patients should be considered as evidence of drug effect; comparisons should be made on the basis of these two groups only.

At present four groups of agents are used with a significant degree of effect in the treatment of patients, particularly children, with acute leukemia. They are, in chronological order of discovery: (1) The folic acid antagonists (1947), (2) ACTH (1949), (3) corticosteroid substances (1949), (4) purine antagonists (1952).

The first and fourth are classified as antimetabolites. The second and third belong to the group of hormones and hormone analogues. A number of agents that had shown antineoplastic activity in animal screening studies or in man against tumors other than acute leukemia have undergone clinical trial, but have been found ineffective.

2. Antimetabolites

A. *Folic Acid Antagonists.* No attempt will be made to restate the facts set forth in the section on folic acid antagonists.

During the period when the folic acid antagonists were the only antileukemic agents available (1947–1949), up to 70% of children treated responded with a significant degree of improvement (Farber, 1955a). The percentage of complete remissions achieved varied from 9–66.6% according to various investigators as set forth at the "Second Conference on Folic Acid Antagonists in the Treatment of Leukemia" held in Boston on March 11, 1951. The dosage of the folic acid antagonists has not lent itself to a simple expression in milligrams per kilogram. It has been noted that children often tolerate larger doses than adults and an individual's tolerance has been noted to vary significantly over a period of time. In general it may be said that the patient does not develop increasing tolerance but that often successively smaller amounts will prove toxic. This phenomenon together with the ability of leukemic cells to develop resistance (which may be considered ultimate tolerance) defines the limitations of therapy. Other observations suggest that the tolerance of the patient varies with the amount of leukemic involvement present, the acutely ill child tolerating larger doses than the same child in remission.

The range of the usually used dosage for Aminopterin is from 0.25–1.0 mg./day and for Methotrexate from 2.5–7.5 mg./day. They are given orally whenever possible but intramuscular or intravenous injections may be preferable in special situations. The dosage is the same for all routes. The earliest toxic effects are stomatitic ulcers, often preceded by a hyperesthesia of the oral mucosa to acid solutions. If administration of the agent is stopped immediately the lesions will heal in a few days and therapy may be resumed, preferably at a slightly lower dosage level. Folic acid and the citrovorum factor (folinic acid, leucovorin) have been investigated for their ability to prevent or repair toxic lesions. Burchenal and Kingsley-Pillers (1951) showed that as little as 3 mg. of citrovorum factor intramuscularly daily can prevent toxicity from excessive oral doses of Methotrexate. Schoenbach *et al.* (1950) reported significantly better repair of toxic lesions when folic acid was given in large amounts. Similar acceleration of healing of stomatitic lesions was reported by Farber (1952, p. 171) with citrovorum factor. Several investigators have shown that folic acid and citrovorum factor are capable of inhibiting the toxic effects of antagonists in microbiological systems and animals (Oleson *et al.*, 1948; Burchenal and Babcock, 1951; Broquist *et al.*, 1952; Goldin *et al.*, 1952; Sauberlich, 1953; DeRenzo and Dessau, 1954). There has been no evidence found for the hope that the toxic effects and the antitumor activity may be separable. It must be assumed that inhibition of the former also results in negating the latter. Animal studies supporting this concept have been reported by Burchenal *et al* (1949a, 1950a). Other toxic effects which will occur only if clinical supervision is lax or if

therapy is intentionally pushed beyond the stomatitic stage will include ulcerations of other mucosal surfaces, usually of the small intestine occasionally accompanied by bleeding, and finally a severe depression of the bone marrow will be achieved with hemorrhagic phenomena, anemia, and infections. Taylor *et al.* (1950) have described the most severe toxic changes. Alopecia is occasionally noted but has not been found a reliable index of toxicity since continued therapy in patients showing it as sole manifestation failed to proceed to more severe symptoms. Dermatitis medicamentosa has been noted in rare instances.

The beneficial effects of therapy usually will be noted after three weeks of treatment, though more rapid effects have been observed. An occasional patient may require six weeks of therapy before the full benefit is reached. Continuation of administration of these agents beyond this period in the face of failure to induce a response is unlikely to lead to further improvement. Children have been found to respond much more favorably than adults and the ratio of complete remissions for the childhood versus the adult age group is about 6 to 1. The duration of complete remissions has varied from some lasting but two weeks to one instance of remission induced with Aminoteropterin (4-aminopteroyltriglutamic acid) in October, 1949 in a then 3-year-old boy which is still continuing on constant therapy with Methotrexate (now 6¼ years). The median length for all complete remissions is about 8 months.

Until recently there were two schools of thought concerning the management of the patient once a remission had been induced. Intermittent therapy meant inducing a remission, then stopping treatment until relapse occurred, then starting treatment again and to repeat this cycle until no further improvement could be achieved (Pierce and Alt, 1948; Stickney *et al.*, 1949; Mills *et al.*, 1950; Burchenal *et al.*, 1951). Smith and Bell, 1950 modified this method by following the bone marrow with weekly aspiration, and stopping therapy when the total nucleated count fell to 30,000. This technique has not found wide acceptance. Maintenance therapy after inducing a remission has been used by Farber *et al.* (1948); this method has been generally adopted. (Wolman *et al.*, 1949; Sacks *et al.*, 1950; Rice *et al.*, 1950; McLean, 1951; Wolman *et al.*, 1952; Schoenbach *et al.*, 1952.)

B. *Purine Antagonists.* Hitchings and his co-workers began studies into the purine and pyrimidine requirements of microorganisms in 1942 and investigated their role in the biosynthesis of nucleic acids (Hitchings and Elion, 1954). Since an intimate relationship between folic acid and purine and thymine metabolism appeared likely (Stokes, 1944) a study of purine and pyrimidine antimetabolites seemed promising.