APPROACHES TO TUMOR CHEMOTHERAPY

A symposium of papers and discussions on various aspects of tumor chemotherapy, developed from the summer meetings of the Section on Chemistry (C) of the American Association for the Advancement of Science at Gibson Island, Maryland, 1945–1946

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FOREWORD

THIS volume contains (a) the papers and revised discussions presented at the 1945 AAAS-Gibson Island Research Conference on Tumor Chemotherapy, (b) the papers of the 1946 Conference that relate directly to this subject, and (c) various other invited papers designed to round out a fairly representative view of the present status of the field of tumor chemotherapy. Papers of the 1946 Conference not contained in the present volume, because they were not concerned with chemotherapy, are abstracted in *Cancer Research,* Volume 7, Number 1, January, 1947.

A previous volume covering the papers and discussions of the more general AAAS-Gibson Island Research Conference on Cancer held in 1944 was published in 1945. The Foreword to this previous volume contains many remarks pertinent to the present volume, particularly with reference to an informality of presentation aimed at preserving some of the atmosphere of the conference room. In both volumes emphasis has been placed on individual, rather than collective, responsibility of the speakers and discussers for their respective contributions. Many of the contributions have undergone extensive post-conference amplifications or deletions by their respective authors, but have been subject to a few editorial changes. It is a noteworthy feature of these important research conferences that they involve not only extensive poolings of results but catholic clashes of opinion, and it is but natural that the participants in the conferences, as well as readers of this volume, will have widely varying judgments as to the relative interest and merits of the various facts, opinions and outlooks presented.

The field of tumor chemotherapy has as yet so little of ultimate solution to offer, compared with its possible promise, that it has not been easy to arrive at a strictly logical grouping of the papers, but an attempt has been made, following an historical introduction, to proceed from animal to human experimentation insofar as the distinction is feasible. This order also corresponds largely with the order of presentation and the availability of the contributions. The discussions relate mainly to the papers on animal studies, reported for the most part in 1945. The section on Nitrogen Mustards represents a nearly complete account of all work available to date. Certain of the clinical material represents new experimentation of a type never reported previously elsewhere. The papers as a whole describe and collate almost all of present-day methodology in tumor chemotherapy.

The ultimate solution of the problem of human cancer will probably rest largely on a molecular, that is, chemical basis. Agents —exogenous and, in instances, endogenous chemical molecules—will be required that can reach effectively every cancer cell in the body. In this respect the knife and the ray have their definite limitations as centuries and decades, respectively, have demonstrated. The hope for the molecular approach lies mainly in the finding of modern biochemistry that whereas etiologically and morphologically cancer represents a great group of diseases, biochemically it presents a surprisingly uniform metabolic, chemical pattern that is characteristic, and therefore potentially subject to a unique or reasonably small number of chemotherapeutic agents, just as large classes of pathogenic microorganisms now are. The established biochemical "much of a muchness" of cancers may be regarded as a by-pass to an otherwise seemingly endless complexity of the problem. It is to be hoped that this horizontal, rather than ver-

tical, approach to tumor chemotherapy can do much to offset past pessimism and disappointment over accomplishment to date. The present volume, a progress report, is addressed largely to future workers, some possibly scientifically yet unborn, who will respond to the spur of the negative and the spire of the positive.

In acknowledgment, the expense of recording the discussions and certain of the papers at the 1945 Conference was provided for by a grant from the Jane Coffin Childs Memorial Fund for Medical Research. Special thanks are due to Mrs. Olive Crow Luria, of the Master Reporting Company, for her skilful and painstaking stenotypic recording and transcription, and to Mrs. Florence H. Hitzel and Miss Marie L. Hesselbach for their editorial work in collating the manuscript-discussion material.

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GENERAL REVIEW OF CANCER THERAPY

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NEARLY one hundred years ago Otto Völker (cited in Wolff 1914) wrote the following sentence: "The degree to which a disease is open to therapeutic attack is inversely related to the number of remedies that we possess."

Nowhere is this more true than in cancer, for which treatments have been advanced by the thousand. The older ones included crabs or crab soup, no doubt an early application of the mistaken principle that like cures like; purgation; diet; hyperemia and its opposite, blood-letting; salves, black at first and later, if this proved ineffectual, red; caustic pastes; plasters; pipe clay; blood-cleansing teas; silver and gold; mercury; copper; phosphorus; arsenic, externally and internally; narcotics; compression; cold, long before the recent venture into cryotherapy; acids; alkalies; metals in the colloidal state; electricity; diuresis; diaphoresis; vegetable products of all sorts, including violet leaves; and toads.

If we have no cure today, surely it is not from lack of trying. But all these old remedies, often amusing and always interesting to the medical historian, are without value for the modern investigator and therefore we shall begin our review of therapeutics with the establishment of modern cancer research at the opening of the present century. Obviously a complete survey is impossible, for the number of articles must run well into the thousands. Hence only a few have been selected, which are more or less representative of both the good and the bad.

Those who have not been trained in chemistry or medicine, which after all is only applied chemistry, may not realize how difficult the problem of treatment really is. It is almost—not quite, but almost—as hard as finding some agent that will dissolve away the left ear, say, yet leave the right ear unharmed: So slight is the difference between the cancer cell and its normal ancestor. Metastases in the brain from a cancer of the liver continue to secrete bile despite the fact that they have undergone a significant change of some sort, and are now growing on a foreign soil besides; a carcinoma of the tongue goes on making keratin, the natural product of squamous epithelium, and so on. It was observations such as these that finally disposed of the hypothesis according to which the malignant cell is a cell that has lost the habit of work and gained the habit of growth.

When the experimental era opened in earnest, shortly before 1900, the first attempts at cure followed closely the paths that already had been marked out by the developing sciences of bacteriology and immunology. The presence of some sort of antibody in the serum of mice resistant to transplantation was at once suggested when Clowes and Baeslack (1905) reported that exposure of cancer cells to immune serum before inoculation inhibited their subsequent development. Few investigators were able to reproduce this result, however, and attempts to elicit a specific immune serum by inoculating foreign species with mouse tumors were no more encouraging. After several years of vain effort Russell (1908) came to the conclusion that there are no features in resistance to transplantable tumors comparable to the antibodies evolved against the infective microorganisms; and Jensen (1909) finally admitted that when he had ascribed healing properties to the serum of rabbits treated with mouse cancer it had not been known that propagable neoplasms often regress independently of any treatment whatsoever.

This they do because they are composed of the cells of one animal growing in the

* Delivered Aug. 1, 1945, morning session.

body of another. But any immune reaction that they excite seems to be directed against the proteins of this first animal, and not specifically against the cancer cell as such. It was a hard, hard lesson, and articles on resistance still appear from time to time, though until very recently the consensus has been that nothing is to be anticipated from immunity. The past few months, however, have seen an article or two suggesting that this chapter may not be entirely closed, and one of the foremost of English immunologists said in a personal letter several years ago that he had not yet abandoned all hope of a specific reaction on the part of the cancer cell. Nor is Oberling (1944) entirely in despair. Current methods of preparing cytotoxic sera are rudimentary in the extreme, he writes, and future research must endeavor to isolate from cancer some proteins, or other substances, that will be more specific in producing antibodies. Maybe the problem will be solved, he continues, by the injection of something that can combine with certain constituents of the cancer cell, for modern immunology has shown the possibility of creating in this way complexes against which specific antisera can easily be made, and there seem still to be opportunities.

Well, such optimism is the mainspring of research. The blood is a marvelous fluid, said Goethe, in *Faust;* how marvelous he never suspected when he wrote these words, and perhaps it will turn out to be even more marvelous than we ourselves now realize.

Many of the early experiments were vitiated by the fact that the materials under investigation were injected into or near the neoplasm, a procedure that almost everyone nowadays has learned to avoid. This applies to Reicher's treatment with adrenalin (1910), to Uhlenhuth and Weidanz's with pyocyanase (1909), to Beck's with preparations of bacteria or their metabolic products (1911), to those of Spiess (1907) with various anesthetics, and to far too many others. The woman with cancer of the breast and pulmonary metastases that could by no feat of magic be injected, was lost sight of, as was the elementary fact that a tumor accessible to injection is usually accessible to surgery.

Tumors or Their Extracts or Autolysates

Perhaps on the principle of setting a thief to catch a thief, tumors themselves have been used for treatment after having been prepared in various ways.

Barratt and Gelarie (1913) reported that frozen mouse tumor inhibited the growth of implanted carcinomas in about one-third of the mice treated, and that a somewhat similar result had been achieved with unfrozen fetus and placenta. It may be that the experiment would never have been published, however, if there had been some controls.

Tumor autolysates were employed by Lewin (1912) and by Blumenthal (1912), among many others. Both reported favorable results with rat sarcoma, but it was not fully realized at that time how prone transplanted sarcomas are to regression, and shortly afterward Keysser (1914) wrote that autolysate therapy had no real cures to its credit in either experimental or clinical medicine.

Fränkel and Fürer (1915), after citing the negative results of several other investigators with press juice from tumors, said that in their own experiments it had shown neither an immunizing nor a therapeutic effect on transplanted growths of the mouse and rat.

In discussing his treatment of cancer in man with serum, leucocytes, and so on from rabbits or sheep injected with human tumors, J. W. Vaughan (1914) expressed a doubt that any method of specific therapy would be of use in the case of large neoplasms; in other words, where it was most desperately needed.

The so-called vaccination treatment employed the whole tumor, rather than any of its fractions. After removal from the patient it was ground, or exposed to antiseptics, or irradiated, in order to kill or at least to devitalize its cells and thus to guard against the danger of implantation when they were returned to the patient's body

by injection. But Coca, Dorrance and Lebredo (1912) were unable to record a single instance of regression of a neoplasm in man as a result of this treatment, and Wood and Prigosen (1925) were strongly of the opinion that experimentation of this sort should be abandoned immediately as not only useless but positively dangerous and wholly unjustifiable from a scientific point of view. It was abandoned.

Organotherapy

The foremost exponent of this form of treatment was Fichera (1935), who developed what he called the theory of "oncogenic equilibrium," since the reticuloendothelial system was supposed to maintain some sort of balance in the body that prevented the formation of a maligant growth. As it was assumed that extracts of one "antiblastic" organ alone would never suffice to cure growths of different origin and different type, Fichera employed spleen, thymus, bone marrow, and lymph nodes from young cattle. No one was able to duplicate the results that he described with his preparation, IG 365, and the treatment should have fallen into oblivion. But it did not. Such is the optimism of the human race that after some 30 years of failure, by almost innumerable investigators and with foreign blood or extracts of the various organs, Blumenthal (1933) and Jacobs (1933a) introduced an extract made from the liver, pancreas, duodenum, and spleen of freshly slaughtered animals. The mixture, JB 5, was used in the form of tablets or salve and remarkable effects were ascribed to it in animals and man by Jacobs (1933b).

A few years later Blumenthal, Jacobs and Rosenberg (1936) announced a new mixture, to which stomach had been added. It was called "Aristotrop," and was said to be highly efficient, but though details respecting its preparation were asked for, they were refused.

Optimists may have found some encouragement in a paper by Cailliau (1936), for he described changes in the vessels and nerves of tumors that were regressing in consequence of the treatment. He referred cancer to the sympathetic nervous system, but the abstracter of his paper remarked acidly, in the American Journal of Cancer, that if the treatment was no better than the theory cancer would still remain an efficient agent in the destruction of the human race. In a subsequent article Cailliau (1938) admitted that renewed experimental and clinical investigation had proved conclusively that the treatment was valueless, and that the histological changes ascribed to it had not been observed in later material. He closed with a caution against using his earlier statements as a scientific basis for the administration of a worthless remedy, and other investigators, too, reported that Aristotrop had no effect on malignant neoplasms. Nevertheless, I have heard that it is being tried in a New York hospital.

A somewhat similar preparation is Braunstein's "Splendothelan" (1933), made from spleen and other reticuloendothelial tissues on the immortal but mistaken hypothesis that the spleen is antagonistic to malignant growth. It has been inoculated time and time again with success, tumor cells and spleen have been reported growing side by side in the egg, yet the delusion persists. Similar in source to Aristotrop, Splendothelan has been found by most investigators to be similar also in its lack of efficacy.

Still another biological product is H 11, extracted from the urine and introduced by Thompson and his associates (Thompson, Holt, Jones, Haydn and Kennedy 1941). It has been tried by Gye, Ludford and Barlow (1943) and by many others on both human patients and animals bearing various types of neoplasms, in most cases with entirely negative results.

Enzymes

In summarizing the relations between tumors and enzymes Stern and Willheim (1943) said that even though neoplasia should prove to be intimately associated with enzymatic disturbances, the concept that such a disturbance, necessarily intracellular, could be counteracted by the ad-

ministration of one enzyme or another is naive in the extreme. Nevertheless, various enzymes have been tried, among them trypsin, lipase, and amylase.

The proteolytic ferments of *B. histolyticus* were injected directly into rat tumors by Torrey and Kahn (1927), with destruction of the growth in from 50–75% of the animals, and more recently a variant of this method has been employed by Connell (1936). It was said that 53% of 382 patients with hopelessly inoperable malignant growths were still living one year after beginning treatment, but Ettinger (1937) reported from Connell's own laboratory that the preparation had no effect upon the growth of a mouse carcinoma, and it was found inactive against other mouse tumors by Gye (1935); also against mouse and rat tumors by Rusch and Preston (1936), and against the Brown-Pearce rabbit carcinoma by Pommerenke (1936).

From Japan came "Carcinolysin," a plant enzyme or enzyme-like substance mixed with oil. Subcutaneous or intramuscular injection into tumor-bearing rats and rabbits, or human patients, was said by Matsushita (1924) to result in necrosis and gradual resorption of the growth. Thirty-five per cent of 3,417 patients were asserted to have been clinically cured and others improved, but apparently this enviable record was not maintained, otherwise we should not all be here discussing the treatment of cancer.

Metals

A good review of the early chemotherapeutic experiments is that of Weil (1915). The list of metals that have been tried reads like a list of these elements in a textbook. Among those whose effects have been investigated with conflicting or negative results are: calcium, magnesium, caesium, barium, iron, cobalt, copper, platinum, silver, gold, mercury, aluminum, thallium, samarium, neodymium, lanthanum, yttrium, scandium, rhenium, tin, tungsten, bismuth, and lead.

Among all the members of this impressive array it is the lowliest, lead, that has received the most attention. Employed since antiquity in the treatment of cancer, its use was revived by Blair Bell because it has a deleterious effect on the chorion, whose cells are invasive, and described by Bell (1924) as "essentially malignant." But there must have been something wrong with the theory, for those who work with lead in its various forms are not conspicuously exempt from cancer. Furthermore, Glynn (1926) could find no histological evidence that lead had any effect on the majority of human tumors treated with it, and in transplanted rat tumors Wood (1926) discovered no sign of a direct toxic action on the neoplastic cell; whatever damage there was followed thrombosis. After a few excited years, and a few apparent miracles, the treatment was abandoned because it proved ineffective in the great majority of cases, and was positively dangerous besides.

Glycolysis

Warburg's theory (1926) that under certain conditions of inadequate oxygen supply only those cells can survive which, having a high glycolytic activity, are independent of oxidative respiration and able to meet their energy requirements by fermentation, has led to a number of therapeutic attempts. The most extensive were those of Fischer-Wasels (1929), but his method, which involved the administration of oxygen and carbon dioxide together with drugs to stimulate oxygen consumption, was complicated, the apparatus elaborate, and the outcome disappointing.

The problem has been approached, also, by keeping tumor-bearing animals in atmospheres where the oxygen pressure was increased as much as five times. Notwithstanding a few favorable reports, Campbell (1937) found that the growth of several varieties of transplantable mouse and rat tumors not only was not inhibited, but was occasionally stimulated. The poisonous effects of the oxygen were decreased by starving the animals for two or three days. The opposite experiment was carried out by Warburg, Wind and Negelein (1927), who kept tumor-bearing rats for 40 hours in an atmosphere containing the minimum

amount of oxygen that they could tolerate. Much of the neoplasm was destroyed, but the cells at the periphery remained alive and continued to proliferate, a result that was confirmed by Campbell and Cramer (1928).

Instead of adjusting the oxygen tension at normal pressure, Sundstroem and Giragossintz (1929–1930) reduced the total pressure to as little as 300 mm of mercury in some experiments. They recorded definite regression of established carcinomas and sarcomas in from 24–83% of the treated rats, but the mortality ran from 14–38%. Furthermore, sarcoma grafts inoculated just before the animals were put into the tank took in 100% of the cases and grew progressively, though this must have been the most vulnerable period in the life of the tumor. Similarly, Rhodenburg (1941) found mouse sarcoma 180 as well as spontaneous mouse carcinomas entirely unaffected when their bearers were kept in a mixture of oxygen, nitrogen, and carbon dioxide at a pressure of 380 mm of mercury.

The most recent experiment of the sort is that of Pollack, Taylor and Sortomme (1942), who reported that a transplanted mammary carcinoma of the mouse was not influenced by increased atmospheric pressure, decreased pressure combined with, or without, periodic starvation, or even by the presence of large bubbles of oxygen in the tissues surrounding the tumor.

Innumerable other attempts have been made to interfere with aerobic glycolysis. Thus Mendel (1937) named 4 substances that will inhibit it: fluoride, monoiodo-acetic acid, glyceric aldehyde, and ferricyanide. The first two are toxic, the third is rapidly destroyed in the blood stream, so that only ferricyanide is available. Mendel described some experiments *in vitro* and suggested that sodium ferricyanide be tried *in vivo*, since it acts exclusively on aerobic glycolysis, which he called the characteristic mettabolic disturbance of the malignant cell.

But sodium cyanide had been tried about 30 years previously by Bullock (1916–1917) and found inoperative, as were the oxidative stimulants sodium iodoxybenzoate and sodium iodozobenzoate.

In a review of tumor metabolism Dickens and Weil-Malherbe (1943) wrote that tumors in general have not only a moderately high aerobic glycolysis, but a high anaerobic glycolysis as well, combined with a respiratory quotient below unity. This is Burk's view (1937) also, for he defines a tumor as "a growing glycolyzing tissue with a deficient respiration." But the problem of treatment along these lines turns out to be not so simple as it seemed at first, particularly as some normal tissues have a metabolism approaching that of the neoplasms. This is eminently true for the intestinal mucosa of the rat, which, according to Dickens and Weil-Malherbe has a glycolytic and respiratory activity comparable with that of the most vigorously growing neoplasms, combined with a respiratory quotient of 0.85.

Fever Treatment

Having observed the arrested evolution of malignant growths in 4 patients with temperatures above 104°, Vidal (1910) daily exposed tumor-bearing mice to a temperature above that of the normal organism and reported degenerative changes in their growths.

Woglom (1934) described similar alterations in various neoplasms of rats and mice after their temperatures had been raised to as high as 104° in some cases, but the liver and kidneys were seriously damaged; and despite their appearance under the microscope the tumors continued to grow. The experiment was done in order to see whether short-wave therapy had some specific effect other than that due to mere heating of the tissues, as Reiter (1933) maintained, or whether the results described could be referred simply to the raised temperature, as Schereschewsky (1933) asserted. The question remained unanswered, however, for there were no results, as has already been said. The tumors continued to grow.

In this section may be included Braunstein's treatment (1933) by means of fever induced with artificially inoculated malaria,

though it was sought at the same time to stimulate the reticuloendothelial system. Here, too, though it was not exclusively a fever therapy either, may be mentioned Coley's bacterial toxins, which may be passed over now since they will be referred to later by Dr. Shear and his associates. Braunstein wrote that cancer is 15 times as frequent in malaria-free Denmark as in malaria-ridden Serbia, but this does not mean that malaria protects against cancer, as he said it does; it means nothing more than that the physicians and vital statistics of Denmark are 15 times as good as those of Serbia, for cancer is found in man and beast wherever it is skillfully sought.

Cryotherapy

Cold, too, has been employed in the treatment of cancer. Smith and Fay (1939) suggested its trial because of the relative infrequency of primary and metastatic carcinoma in those parts of the body with a low temperature, as compared with those where an optimal high temperature is found. They reported degenerative changes in the neoplasm, and relief from pain, after local or general refrigeration. However, Bischoff, Long and Rupp (1940) found that induced hibernation, as the treatment was sometimes called, had no permanent deleterious effect on the growth of either sarcoma 180 or spontaneous mouse carcinomas, and A. M. Vaughn (1940) described its employment in man as hazardous and unjustifiable. In brief, after a fair trial cryotherapy turned out to be only one more in an interminable series of disappointments.

Dyes

Weil (1916), one of the first to investigate the possibilities of dyes as therapeutic agents, tried over 20 members of the benzidine group on rat tumors, with discouraging results. He expressed the opinion that dyes will not penetrate healthy cytoplasm, and criticized the assertions of v. Wassermann, Keysser and Wassermann (1911), who had employed eosin as a carrier for selenium because, they said, it penetrates all the cells of the body.

Equally disheartening results rewarded the efforts of Simpson and Marsh (1926), who treated mice bearing spontaneous mammary carcinomas with some thirty coal tar dyes. Simpson (1928) later extended the list to 144, but reported that none was effective.

Isamine blue attracted some attention for a time. Bernhardt and Strauch (1928) recorded arrest of growth and even some regression in a considerable proportion of 33 patients with inoperable neoplasms after intravenous injections of this dye, thus confirming a statement of Roosen (1924). But Kreuzwendedich von dem Borne and Ten Seldam (1932) saw no effect upon tar tumors of the mouse, or upon the origin or course of spontaneous new growths in this species, and they were not alone in their failure to confirm the earlier reports on the favorable action of isamine blue.

Snake Venoms

The most used has been that of the cobra. Despite some premature encouraging reports it has no effect on the cancer cell, and even its reputed power of relieving pain is nonspecific, irregular, and uncertain.

Vitamins

These may be dismissed with scant courtesy. An enormous amount of investigation has been lavished on these accessory foods that are so dear to the public—dear in both senses of the term—but none has been found to have any curative value, though there is some evidence to show that yeast will prevent the development of carcinoma of the liver in rats fed *p*-dimethylaminoazobenzene. This appears, however, to be a special case.

Heptylaldehyde

Starting from the observation that oil of wintergreen, fed daily to mice with a high incidence of mammary cancer, delayed the development of these neoplasms and lowered their incidence, Strong (1938a and 1938b) sought for the active agent in the oil. It was found in the fraction with a low boiling-point and was eventually iden-