ONCOLOGY 1970

Being the Proceedings of the
Tenth International Cancer Congress

Volume II

Experimental Cancer Therapy

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WITH THE COOPERATION OF THE
OFFICIALS OF THE TENTH INTERNATIONAL CANCER CONGRESS

YEAR BOOK MEDICAL PUBLISHERS · INC.
35 EAST WACKER DRIVE · CHICAGO

Library of Congress Catalog Card Number: 70-150262

International Standard Book Number: 0-8151-1764-7

Acknowledgments

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Acknowledgment is made of the kind services of Dr. Clifton D. Howe, Associate Director for Clinics and Chief of Clinics, Dr. Darrell N. Ward, Head, Department of Biochemistry, and Dr. Felix L. Haas, Head, Department of Biology, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston for their assistance in arranging the contents of the volumes. The help of Miss Donna McCormick and Mrs. Marilyn Cavanagh of the Congress' Secretariat is gratefully acknowledged.

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In Appreciation

Special contributions in support of the Tenth International Cancer Congress have been made by the following:

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We are especially indebted to the CALOUSTE GULBENKIAN FOUNDATION which provided funds and support for the publication of the Proceedings of the Tenth International Cancer Congress.

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Foreword

THE TENTH INTERNATIONAL Cancer Congress, held in Houston, Texas, U.S.A., May 22 through May 29, 1970, was attended by 6,018 physicians and scientists from throughout the world. Of these, 1,957 participated in the sessions. The speakers, representing 72 different countries, presented 1,740 papers; abstracts of 1,342 proffered papers appeared in the book of *Abstracts,* copies of which were distributed at the Congress. The remaining 398 papers appear *in toto* in the five volumes comprising this set of Proceedings. These 1,740 papers were virtually all of the papers submitted for presentation; less than a dozen titles were rejected. Consequently, one might reasonably assume that these papers and abstracts comprise a comprehensive survey of the international status of the science and art of oncology as it existed in the spring of 1970.

The papers, speeches, and lectures may be divided into seven general groups:

1. Congress Ceremonies
2. Preliminary Special Sessions of the Congress
3. Main Congress Panels
4. Postgraduate Course Panels
5. Proffered Paper Sessions
6. Rapporteur Reports
7. The Harold Dorn Lecture

The sequence in which these various presentations were made, their authors, and the organization of the Congress may be found in the *Program* of the Tenth International Cancer Congress (Library of Congress Card Catalogue No. 42-43259). The members of the Congress, i.e. those who registered at the meeting, and the names and addresses of most of the persons who presented papers may be found in the *Members* of the Tenth International Cancer Congress (Library of Congress Card Catalogue No. 73-124104). Abstracts of papers presented at the Proffered Paper Sessions (No. 5 in the general groups listed above) are contained in the *Abstracts* of the Tenth International Cancer Congress (Library of Congress Card Catalogue No. 70-12413). All three of these volumes were published by The Medical Arts Publishing Co., 1603 Oakdale St., Houston, Texas, U.S.A. 77004.

The papers published in the 5 volumes comprising the published

proceedings include the Congress Ceremonies (No. 1 in the above list), the Preliminary Special Sessions (No. 2), the Main Congress Panels (No. 3), the Postgraduate Course Panels (No. 4), the Rapporteur Reports (No. 6), and The Harold Dorn Lecture (No. 7). The papers have not been published in the order in which they were given at the Congress, since during the Congress several presentations occurred simultaneously. Rather, in these volumes, the papers, including the Rapporteur Reports and The Harold Dorn Lecture, have been assembled into groups of related subject matter.

Because of the overwhelming number of citations contained in the reference lists submitted by the authors, it was not possible to verify the citations or to complete those submitted in abbreviated form. Therefore, the reference lists have been published in much the same way in which they were received. In the few instances in which no reference list was submitted, or when the list was excessively lengthy, an editorial note has been added, directing the reader to apply directly to the author for a list of the literature cited.—Editors.

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Experimental Models and Clinical Trials: Screening Methodology

Historical Review and Perspectives

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THE EARLY HISTORY of cancer chemotherapy has been amply reviewed[1] and need not be considered in any detail here. Before World War II, small-scale drug development programs were being conducted by Boyland in Great Britain, employing spontaneous breast tumors of mice, by Furth in the United States, using experimental leukemia, and by Lettré in Germany, using tissue culture and ascites tumor. Shear, in 1930, had established a screening program employing sarcoma 37 in which bacterial polysaccharides were tested for their capability of producing hemorrhage and necrosis.

Strong impetus for chemotherapy screening was provided with the demonstration that nitrogen mustard was biologically active and efficacious in treatment for malignant lymphoma.[2, 3] The screening programs gathered momentum following the demonstration by Farber that the folic acid antagonist, aminopterin, was capable of inducing remission in children with acute leukemia.[4] Initial major screening programs were developed at the Sloan-Kettering Institute by Rhoads, Stock, and Burchenal, at the National Cancer Institute with the extension of Shear's program to encompass synthetic compounds and plant products, at the Chester Beatty Research Institute in London by Haddow, at the Cancer Institute in Moscow by Larionov, at the University of Tokyo by Yoshida, at the Children's Cancer Research Foundation in Boston by Farber, and at the Southern Research Institute by Skipper.

Additional chemotherapy test programs were developed at pharmaceutical houses, research institutes, and medical schools, and are too numer-

ous to list. Subsequently, and as a logical development, with the establishment of the Cancer Chemotherapy National Service Center at the National Cancer Institute (NCI), a well-organized national screening effort was undertaken under the helm of Endicott and, more recently, under Zubrod, which has been developed into a comprehensive chemotherapy program involving the entire spectrum of chemotherapeutic endeavor ranging from the acquisition and testing of new compounds through drug development, preclinical pharmacology, and chemotherapeutic investigation.[1] The screening program of the NCI as an integral portion of the total chemotherapy effort is well coordinated with testing programs in this country and abroad.

What are the attributes of an appropriate screening program? Basic to the success of any chemotherapy program is the validity of the underlying methodology. Any screening program, to be successful, must have certain requisite characteristics. The screening program must be sufficiently quantitative so that it is capable of identifying new agents as active. Any demonstrated activity should be reproducible. The screen should be neither so sensitive that it selects too many agents as positive nor so insensitive that potentially useful compounds fail to meet the criteria for activity. Most important, the screen should have specific relevancy to the clinic. The most desirable screen is one which selects compounds that have a strong likelihood of being active in treatment for clinical neoplasia.

Initially in the Cancer Chemotherapy National Service Center (CCNSC) program three animal tumor systems, namely, leukemia L1210 (L1210), sarcoma 180 (S-180), and mammary adenocarcinoma 755 (CA-755), were employed for screening.[5] These screening systems had been selected following a comprehensive analysis by Gellhorn and Hirschberg.[6] In this analysis, the action of 27 compounds was examined in 74 screening systems, including tumor screens, biochemical and microbiological assay systems, and systems involving differentiation and development. A major conclusion of the study was that the nontumor systems were incapable of replacing tumor systems as screens for antitumor agents. Second, it was indicated that no single tumor system might be expected to detect all of the active antitumor drugs, suggesting that it would be desirable to examine the utility of a spectrum of tumors. Subsequently, in the CCNSC program, in order to obtain a broader experience, some 20 animal tumor systems were employed for routine screening.[7] In general, the drugs were tested against L1210 and two of the other systems selected on an arbitrary basis. In addition, more than 100 tumor systems were retained for secondary evaluation of drugs and for special investigations.

Some 10 years after the initiation of the CCNSC screening program, progress in laboratory drug testing and clinical investigation had resulted in the accumulation of a large body of data which permitted objective evaluation of the relationship of screening programs to the clinic. A ret-

rospective analysis was therefore conducted in the Chemotherapy Program of the NCI in 1966 to determine the predictability value of screening systems for the selection of clinically active compounds.[8] The analysis showed that retrospectively the available screening systems had a good record for signaling clinical activity. In fact, the utilization of a limited number of screening systems, namely L1210, Walker carcinosarcoma 256 inoculated intramuscularly (Walker 256 IM), and the Dunning ascites leukemia would have predicted activity for almost all of the compounds which at that time had been established as active against clinical neoplasia. As the result of this analysis, primary emphasis was placed on screening with the L1210 and Walker 256 IM systems. At present, the Walker 256 IM system has been temporarily removed from routine screening pending the clinical evaluation of a number of compounds with marked activity in this system. Additional studies are being conducted to explore in detail the possible advantages of other test systems. For example, the P-388 leukemia system appears to be suitable and is now being employed in addition to L1210 for the routine screening of natural products. Its usefulness in this area was suggested by the observation that mithramycin, which has not demonstrated activity in the L1210 system, has definite activity against P-388 leukemia. Plant products, such as vincristine and vinblastine, and antibiotics, including actinomycin D and mitomycin C, have been more active against P-388 than against leukemia L1210 (Table 1-1), indicating the possibility that the P-388 system may be useful for the uncovering of crude natural products where the active moiety is in very low concentration.[9] The system may prove to be useful for chemotherapeutic testing during the purification process for natural products.

The B-16 melanoma system is being evaluated for inclusion in the screening program, following detailed analysis of its growth characteristics in which it was determined that the tumor has a relatively long doubling time. It is considered that slowly growing tumors of this type pos-

TABLE 1-1.—COMPARISON OF ACTIVITY RATINGS OF NATURAL PRODUCTS IN LEUKEMIA L1210 AND LEUKEMIA P-388

NSC	NAME	LE % ILS*	P-388 % ILS*
49842	Vinblastine	40	112
67574	Vincristine	39	>135
82151	Daunomycin	58	127
26980	Mitomycin C	40	150
3053	Actinomycin D	45	>175
7365	DON	25	> 90
24559	Mithramycin	13	122
52947	Pactamycin	17	45

* % ILS = maximum per cent increase in mean survival time of animals over controls.[9]

sessing a low percentage of proliferating cells (small "growth fraction") may exhibit a different spectrum of response to drugs than the standard screens, and have the potential for selection of new agents which may be active against slowly growing solid tumors in man.

Leukemia L1210 has not responded to treatment with L-asparaginase. However, leukemia L-5178Y is responsive and is being employed in special studies with L-asparaginase in relation to chemotherapeutic activity, the origin of resistance, immunologic manifestations, and combination chemotherapy, and for studies of the relationship of L-asparaginase to asparagine and other amino acids.[10, 11, 12]

The mouse plasma cell tumor LPC-1 has been employed in special studies of test agents utilizing the parameters of both antitumor response and the suppression of abnormalities in serum and urine proteins as indices of chemotherapeutic activity.[13] The reticulum cell sarcoma 96132 which is sensitive to poly I:C, an interferon inducer,[14] has been employed in special studies of this and related materials.

The Lewis lung tumor appears to be useful in the chemotherapeutic investigation of tumor cell dissemination and metastasis.[15] Following implantation in the hind leg, this tumor metastasizes differentially to the lung where it forms micrometastases within a week. With such a system, it is possible to investigate the influence of drugs on a solid primary tumor and on the micrometastases in the lungs, as well as against advanced lung metastases.

It is abundantly clear that additional tumor test systems, including transplantable, viral- and carcinogen-induced, as well as spontaneous tumors, are worthy of continuing investigation. The development of new and novel pertinent in vivo and in vitro test systems may, indeed, provide important support in the screening effort and in the unraveling of specific problems in chemotherapy.

Compounds may arrive on the screening scene either on an empirical basis or as the result of various levels of reasoned approaches ranging from serendipity through structure-activity analyses to detailed biochemical rationales. In any event, appropriate quantitative screens have been developed for testing these compounds and, as a result of the great interest and effort in chemotherapy in the last 20 years, a reasonable armamentarium of chemotherapeutic agents is now available with proved therapeutic efficacy in the clinic. With these new agents, important strides have been made in the treatment of acute lymphocytic leukemia (ALL), Wilms' tumor, Burkitt's lymphoma, Hodgkin's disease and choriocarcinoma.[16]

Of 39 established clinically active drugs, 28 are nonhormonal agents. Of these 23 would have been detected as active by the leukemia L1210 system. Two additional compounds, Myleran and dibromomannitol, would have been selected by the Walker IM system. L-Asparaginase was negative in the leukemia L1210 system and the Walker IM system but was not tested in Dunning ascites leukemia or CA-755. It is, however,