Fundamental Mechanisms in Human Cancer Immunology

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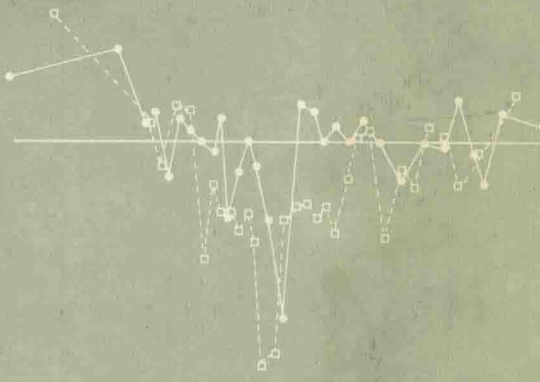

Developments in Cancer Research Volume 5

ELSEVIER/NORTH-HOLLAND

FUNDAMENTAL MECHANISMS IN HUMAN CANCER IMMUNOLOGY

Proceedings of the First International Conference on Fundamental Mechanisms in Human Cancer Immunology, Galveston, Texas, U.S.A., October 27–29, 1980.

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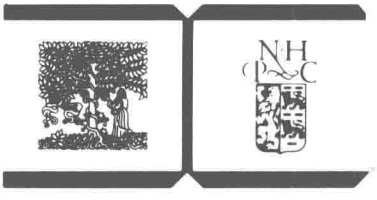

ELSEVIER/NORTH-HOLLAND
NEW YORK • AMSTERDAM • OXFORD

Published by:

Elsevier North Holland, Inc.
52 Vanderbilt Avenue, New York, New York 10017

Sole distributors outside the USA and Canada:

Elsevier Science Publishers B.V.
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Library of Congress Cataloging in Publication Data

International Conference on Fundamental Mechanisms in Human Cancer Immunology (1st : 1980 : Galveston, Tex.)
Fundamental mechanisms in human cancer immunology.

(Developments in cancer research, ISSN 0163-6146 ; v. 5)
Bibliography: p.
Includes indexes.
1. Cancer--Immunological aspects--Congresses. I. Saunders, J. Palmer. II. Title. III. Series.
[DNLM: 1. Neoplasms--Immunology. W1 DE997WM v.16 / QZ 200 F9815]
RC268.3.I463 1981 616.99'4079 81-9845
ISBN 0-444-00648-6 AACR2

Manufactured in the United States of America

FUNDAMENTAL MECHANISMS IN HUMAN CANCER IMMUNOLOGY

DEVELOPMENTS IN CANCER RESEARCH v. 5

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Volume 2—Tumor Progression, Ray G. Crispen—Editor 1980

Volume 3—Neoplasm Immunity, Ray G. Crispen—Editor 1980

Volume 4—Feline Leukemia Virus, William D. Hardy, Jr., Myron Essex, and Alexander J. McClelland—Editors 1980

Volume 5—Fundamental Mechanisms in Human Cancer Immunology, J. Palmer Saunders, Jerry C. Daniels, Bernard Serrou, Claude Rosenfeld, and Constance B. Denney—Editors 1981

Preface

J. Palmer Saunders, Ph.D.

Professor of Pharmacology and Toxicology; Executive Director, UTMB Cancer Research Center; Dean, The University of Texas, Graduate School of Biomedical Sciences at Galveston, The University of Texas Medical Branch, Galveston, Texas

Cancer is probably the most feared of human diseases. The very word "cancer" strikes terror in the hearts of most of us. It is not the fear of dying that frightens us. After all, heart disease and strokes kill more people each year than do malignancies. No, it is the frightening prospect of a prolonged, painful illness resulting in isolation from the rest of humanity, and, frequently, dehumanizing disfigurement produced by heroic surgical procedures aimed at rooting out the disease. Death, when it comes, is regarded as a welcome release from a long period of exquisite torture. Cancer then stands as the great challenge to medical science and to the physicians who must bear the burden of treating its sufferers. Cancer is regarded as a universal evil, and no other disease so stirs the emotions. As a consequence, people use such terms as "crusade" and "war" for the constant battle against the disease. No other disease has the ability to loosen the purse strings both of the federal government and of individual citizens. All of us wish to do all we can to stop cancer and each one of us secretly prays that a cure will be discovered before it engulfs us too.

Cancer is not a single disease—there are probably two hundred different cell types. But it is convenient to speak of cancer as if it were a single entity. Cancer affects most living things and it is part of the life process itself. There is no cell which has a greater will to survive and multiply than the cancer cell. Cancer was well-known even to the ancients, and Hippocrates gave it its name because its pattern of cell growth resembles a crab. The Greeks and Romans thought that cancer was caused by an imbalance in the bodily humors. After 2500 years marked by constant research and study, we still cannot improve very much on that description. In fact, we can state with fair confidence that

cancer in its many manifestations is not a disease but a symptom of a fundamental disorder in the host organism's defense mechanisms.

In the nineteenth century, the diagnosis of cancer was uniformly considered a sentence of death. Great secrecy surrounded the diagnosis and families went to great lengths to prevent it from being known—not only to persons outside the family, but to the victim. Cancer caused great dread and physicians themselves avoided the diagnosis as long as possible—thus surely aggravating the situation. Many persons felt that cancer was a degrading disease and there was fear of "catching" cancer, as if it were an infectious disease. As a result of these various emotions, the cancer victim was often condemned to a lonely and horrifying death. Surgery was the accepted method of treatment. To isolate the tumor and cut it out seemed the only rational approach. And of course this sometimes worked. When a tumor was localized, surgical removal was quite effective. Unfortunately, the majority of cancer victims were not that lucky. Cancer cells migrating to other parts of the body soon began to grow and the disease returned, this time without much hope of a surgical cure.

At the end of the century, with the discovery of Roentgen rays and their effects on living cells, a new modality of treatment was introduced. At first crude x-rays were effective only on superficial lesions, but as the principles of radiobiology were slowly uncovered, more sophisticated techniques were used. With the introduction of more powerful beams, scientists learned how to control the rays—thus avoiding some of the damage to normal tissue and concentrating on the tumor. At its best, however radiation was another form of surgery. Once a tumor was detected—and this was the crucial step—the decision to use surgery or radiation depended more upon the specialty of the oncologist rather than on any rational protocol.

After World War II, clinical groups in Chicago and New Haven attempted a systematic study of the use of nitrogen mustard as a treatment of cancer. Cancer chemotherapy—or the treatment of cancer with various chemical agents—was born out of chemical warfare, and it was not long before other compounds were introduced. Only the leukemias and lymphomas however seemed to be susceptible to treatment with drugs, and even then little success was obtained. Then, in 1955, the proponents of chemotherapy research persuaded the Congress to appropriate large (for that time) amounts of money. Using the successful search for an antimalarial drug to support their case, prominent advocates of chemical treatment argued that it was almost certain that somewhere—on the laboratory shelves of synthetic chemists or among the many biologically active plants of the country—there existed a "magic bullet" which would cure cancer. "Give us $5 million a year for the search and we'll find a cancer cure in 5 years," they claimed. Congress was convinced and established within the National Cancer Institute a Cancer Chemotherapy Service Center to carry out the search for new agents and to screen them against tumor cells. Provisions were also made for the establishment of special clinical teams to try out the expected new compounds in human cancer therapy.

Unfortunately, the hope for a cure engendered by these words proved naive. The oversimplification broke down and researchers belatedly came to realize that the struggle against cancer was far more complex than finding a "magic bullet." Nevertheless, the screening mechanism of the National Cancer Institute produced several new compounds, each of which gave partial promise of activity against the childhood leukemias and lymphomas. Vincent de Vita and his co-workers pioneered the use of complex mixtures of compounds (the MOPP program) and were able to secure long-term remissions in Hodgkin's disease and some leukemias.

During this time, surgical procedures and more powerful radiation therapy were still being employed against the so-called solid tumors (which remain the major killers), since it appeared that chemotherapy was only partially effective in most cases. The use of all three modalities of treatment (multimodal therapy) was gradually introduced in the late 1960's. Today, the treatment of cancer can involve all three therapies, surgery and/or radiation to reduce the tumor's bulk, and selective and appropriately timed chemotherapy to eradicate metastatic foci throughout the body.

The outlook for cancer today is far brighter than it was a generation ago. There are over 1.5 million people in the United States whose cancers can be said to be "cured," as judged by survival five years beyond first diagnosis. It is estimated that better than 30% of the approximately 650,000 new cases of cancer diagnosed each year will be added to this group. Among patients treated in specialized and comprehensive cancer centers, the rate may even exceed this figure. The key to this success is early diagnosis, since few would disagree that the chances for a favorable outcome depend on early detection and diagnosis, followed by aggressive treatment.

Despite improved prognosis for childhood leukemia, lymphomas, and other limited cancers, the mortality data for the major cancer killers—lung, colon, breast, prostate, and bladder—remain alarmingly stable. In fact, for the first time in 25 years, cancer incidence has begun to rise (Pollack and Horm, 1980). Not all of this increased incidence is due to smoking. Cancer epidemiologists claim that even discounting the increased incidence of smoking-related cancer, the overall cancer rate is still on the upswing. Some scientists feel that the tremendous increase in the synthesis of new chemical compounds since World War II and their almost universal employment in all phases of human activity must be tied in somehow to this cancer increase. Marvin Schneiderman, Associate Director of the National Cancer Institute, has stated categorically that these trends "suggest industrial exposure may be contributing more and could contribute substantially to the cancer burden in the future (Wade, 1980). Even if one does not entirely agree with this point of view, it is clear that the ubiquitous chemical carcinogen is with us to stay—in our food, in our water, and in the air we breathe. In the face of this ever increasing danger and in view of the resistance to treatment of the cancers responsible for the greatest mortality, biomedical science should expect an even tougher battle in the future. New concepts must be devised and new approaches employed.

Immunology is the basic science of how the body copes with foreign invaders. It has always been a mystery how a cancer cell can by transformation become a "foreign substance," and yet escape detection and destruction by host defense mechanisms. There are reasons to suspect that malignant transformation is a common occurrence, and that the host's immune system normally operates continually to seek out and destroy these wild cells. According to this hypothesis, it is only when this system becomes defective that cancer cells can establish themselves and multiply. At later stages in its differentiation, the colony may create its own perimeter defense and thus thwart the body's natural immune defense mechanisms. At this point, the cancer emerges as a frank disease entity.

Efforts to employ immunotherapy against cancer therefore cannot be based purely on the administration of additional amounts of substances normally found in the body, such as interferon, unless one can predict precisely at what period the body's defense mechanism needs augmentation. We need to learn much more about basic immunologic mechanisms of normal and malignant cells before we can mount any large scale program of immunotherapy. The purpose of the Symposium is to facilitate and stimulate an exchange among laboratory and clinical scientists who are leading investigators of those basic mechanisms.

Today, we can look forward to many advances in cancer research which were beyond expectation just a few short years ago. The biological revolution that is now in full swing argues convincingly for an eventual solution to the dreadful problem of cancer. That hope, coupled with the great advances already made, should give new inspiration to all of us and impel us to redouble our efforts to uncover the basic principles of cell biology.

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Acknowledgments

This Symposium is the first of a series to be sponsored jointly by The University of Texas Medical Branch, Galveston, Texas and The University of Montpellier, Montpellier, France. The Editor wishes to thank the administration of both universities for their encouragement and support during both the planning of the conference and the meeting itself.

Financial support for the Symposium was provided in part by a Grant from the National Cancer Institute—CA 27958-01A1. The Editor wishes to express his appreciation to the staff of the National Cancer Institute for their support during preparations for the conference. Financial support was also provided through generous gifts from the Harris and Eliza Kempner Fund of Galveston, the American Cyanamid Company, Bristol Laboratories, Eli Lilly and Company, Hoffman LaRoche, Inc., and Stuart Pharmaceuticals. The Editor wishes to convey grateful thanks to these organizations for their additional support, without which it would have been difficult if not impossible to complete arrangements for the meeting.

An international Symposium of this nature is not accomplished without much hard work and dedication from a number of individuals. The Editor would particularly like to express his thanks to the Assistant Editor, Dr. Constance Denney, who worked many long hours in editing and preparing the manuscripts for publication. Thanks are also due to the efforts of the staff of the UTMB Cancer Center—Mr. Fred C. Delaney, Ms. Margie Taylor, Mrs. Karen Lewis, and Mrs. Roxanne Schuster.

If the Symposium has achieved a measure of success, it can be attributed to the excellent presentations by the individuals who participated in the Symposium. The Editor wishes to thank them all for their enthusiasm and vigorous participation in the many fruitful and stimulating discussions which occurred during the conference.

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Cell Membranes