CYCLIC AMP, CELL GROWTH, AND THE IMMUNE RESPONSE

Edited by Werner Braun
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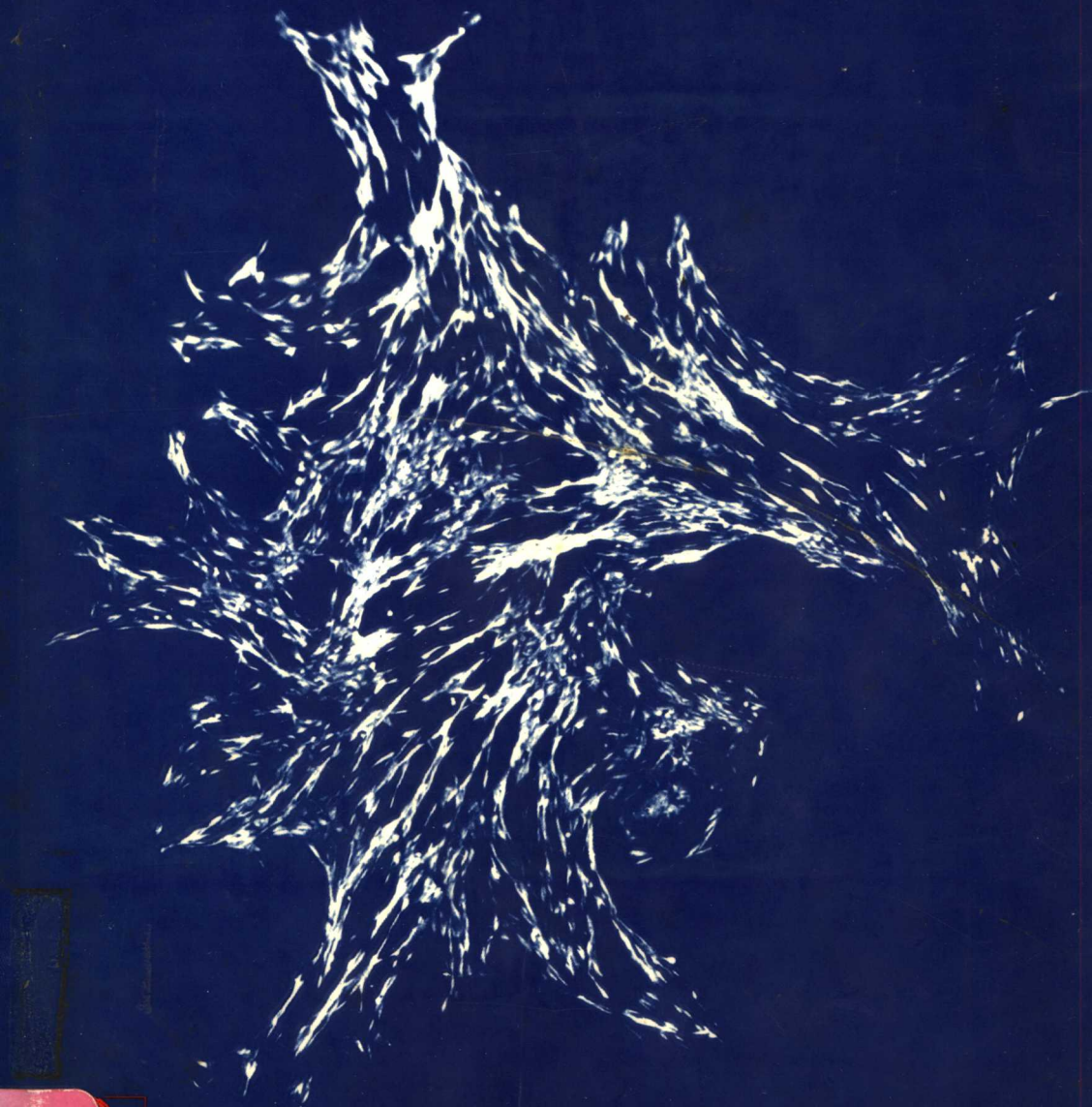

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PREFACE

The brilliant research of Dr. Earl Sutherland and his colleagues has had a broad impact on many areas of biology. Among the fields influenced rather late by the insights arising from this work were immunology and oncology. Although research relating cyclic AMP metabolism to the development and manifestations of the immune response and the control of mammalian cell growth is relatively recent, the growth of knowledge in these areas has been rapid and there is already a considerable amount of empirical information. This conference provided an opportunity to collate and begin to interpret that information. A deliberate attempt was made to bring together investigators nominally involved in immunology, biochemistry, pharmacology, or cellular biology for in many instances parallel observations are being obtained in these fields. For example, the immunologist studying the transformation of lymphocytes by antigens or mitogens is carrying out experiments that are very close to those of the biologist studying the growth of cells in culture; in both cases, the phenomena they observe are modulated by changes in the intracellular level of cyclic nucleotides. Many other examples of closely analogous experiments in different fields could be cited, but perhaps the point is clear.

The meeting was convened for two major reasons: to reap the benefits of cross-fertilization which attend the interaction between different disciplines interested in common phenomena, and to permit interested investigators in several fields to formulate preliminary concepts of cyclic nucleotide control of inflammation, immunologic differentiation, and tumor growth. We hoped by this process to discard nonviable ideas and to project the directions in which future progress might be made.

The meeting was primarily the brainchild of Dr. Werner Braun; it was he who obtained funds from the National Institutes of Health and contacted most of the participants. In November 1972, shortly after meeting with us to finalize plans for the meeting, Dr. Braun died suddenly. His death was a great loss to science and to us personally; we feel privileged to have had the opportunity to organize the meeting with him.

There are many without whose assistance the meeting could not

have taken place. Primary thanks, of course, must go to the National Institute of Allergy and Infectious Diseases for providing funds for the meeting. Dr. Dorland J. Davis, Dr. Maurice Landy, and Dr. Bill Gay of that institute were of particular assistance in many aspects of organizing the meeting, as was Mrs. Gwen Northcutt. Sincere thanks are due as well to the Schering Corporation, Merck, Sharpe and Dohme, and The Nelson Research and Development Corporation for additional funds. We wish also to express our gratitude to Miss Lee Stein, Dr. Braun's secretary, who was able to bring together the arrangements he had made for the meeting, and to Mrs. Anne Sobotka, who helped organize both the meeting and the book.

We owe special thanks to Dr. Otto Plescia, Dr. Braun's long-time associate at Rutgers, who was able to reconstruct from Dr. Braun's notes and papers in progress an up-to-date account of his current research.

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CONTENTS

A TRIBUTE TO WERNER BRAUN

It is with heavy heart that I stand before you today on this occasion. It seems only yesterday that Werner Braun was describing, in his usual enthusiastic way, his plans for this meeting. We were in his room at the Campus Inn in Ann Arbor, where we were attending the Cyclic AMP-Prostaglandin Conference last November. Besides the plans for this meeting, we talked about his extensive travel and seminar activities, his council responsibilities, his family, and his particular concern for the health of his wife, Barbara, and then he asked me to read over two rather large manuscripts he had just written. I remember commenting that I wondered how he managed to do so much. He was indeed a dynamo. Three nights later in Bethesda, he suffered a fatal heart attack.

Werner was born in Berlin on November 16, 1914. During his high school days, he did research on problems of genetics as a guest in the Kaiser-Wilhelm Institut for Biology. He later entered the University of Goettingen, where he received his doctorate in biology.

He had completed three years of medical school at the time he left Germany in 1936. He was a guest investigator in genetics at the University of Michigan for a year before becoming a research associate of Dr. R. Goldschmidt at the University of California in 1937, conducting research on problems of physiological genetics. In 1942, he joined the Department of Veterinary Science at the University of California where he studied problems of bacterial genetics, immunology, and biochemistry.

In 1948, Werner became chief of the microbial genetics branch of the Biological Laboratories, Chemical Corps, Camp Detrick, Maryland, and served in that position until he joined the Rutgers Institute of Microbiology as professor of microbiology in 1955. He remained at Rutgers until his death in 1972.

By any standards Werner's scientific accomplishments were impressive. He was a renowned microbial geneticist who, during recent years, applied microbiological approaches with great originality to the study of cellular immunology and cancer. His studies on microbial population changes, especially in the case of *Brucella,* are classical and led him to investigations of the nature and regulation of immune response with possible application to the control of tumor growth. He is the author of over 200 publications in scientific journals, received the Superior Accomplishment Award of the U.S. Chemical Corps and the Barnett Cohen Award from the American Society for Microbiology in 1954.

Werner was a member and leader of many scientific organizations. He was past chairman of the American Academy of Microbiology, former chairman of the Board of Scientific Counselors of the National Institute of Allergy and Infectious Disease, and a member of the National Advisory Allergy and Infectious Disease Council.

He served as a member of the editorial board of the *Journal of Bacteriology, the American Journal of Hygiene, the Journal of the Reticuloendothelial Society, and Infection and Immunity.* He was past president of the Theobald Smith Society.

He was a member of Sigma Xi, Phi Sigma, the New York Academy of Science, the American Association of Immunologists, the American Society for Microbiology, the Genetics Society of America, the Society for Experimental Biology and Medicine, and the Society for General Microbiology.

Werner also was the editor of several books, a contributor to numerous textbooks and encyclopedias, and the author of *Bacterial Genetics* published by W. B. Saunders in 1953 and reedited in 1965. Several of these books are recognized as classics in their field.

Apart from his many scientific accomplishments, Werner Braun was a remarkable human being. He was a rare person given to deep concern for his fellowman and a great love for science. He had an unusual appreciation of life and enjoyed it fully.

Werner was from the beginning a multidisciplinary scientist preferring to look on life and living things as the sum of all integrated activities. He blended his background of genetics, microbiology, biochemistry, pharmacology, and immunology with an astute ability to conceptualize what was really happening in a living system. Though he read a great deal, he preferred to be in direct contact with people in laboratories everywhere—seeking, questioning, and then synthesizing what he had learned into testable hypotheses.

He was an architect, a visionary often ahead of his contemporaries. He once told me, "The world is full of bricklayers, but there are very few architects." It is sad that there are now even fewer.

In his incessant travels to meetings and laboratories, he sought out those who, like himself, had the ability to perceive, to generate ideas, or who had special talents. Often these were students—no one was more encouraging, no one a better teacher and stimulus to the young. Ideas were the important thing, and Werner recognized that young people abound in ideas. He was recently very concerned about the trend toward reduction in research support for numerous young investigators in favor of increased support to relatively few established investigators.

Life is to be lived; this was Werner's philosophy. He wanted to be where the action was, to experience things personally and most of all to know the people who made life happen.

He was a collector of art, and he had a knack for discovering new artists. He had an interesting collection of Israeli paintings and numerous French works. Always, though, he wanted to know the artist personally, to talk with him, and to know the individual behind the work.

He carried a camera not to photograph scenery, but to photograph people. Some of his character shots, close-ups of faces, are classic. His knowledge of food, fine wines, and restaurants the world over was unusual, and I never knew him to be without his Gude Michelin and the small black book in which he noted superb dishes, wines, hotels, restaurants, and the names of the people who make them so—each a personal friend.

Like many of you here, I could continue to recount the marvelous experiences shared, the meals, the fishing trips, the late night story sessions, the vigorous scientific discussions, but time does not permit.

Let it be remembered that this meeting, like so many others, was conceived by Werner Braun to advance our knowledge and to stimulate ideas. Most importantly for Werner, were the people; he was the catalyst bringing bright people together in a friendly atmosphere with enthusiasm and dedication to generate new understanding. His presence will be felt here and in meetings and laboratories yet to be conceived.

I owe him a great deal, and I will always remember him, as I'm sure you will, a true friend.

ERIC L. NELSON

REGULATORY FACTORS IN THE IMMUNE RESPONSE: ANALYSIS AND PERSPECTIVE

WERNER BRAUN (1914-1972)

I. Introduction

Cellular immunology has made rapid advances in elucidating, on a broad scale, the nature of cells involved in immune responses and the diversity of their functions and products, with appropriate recent emphasis on the differences between cell-mediated responses and humoral antibody formation (1). We have learned much in recent years about the usual need for cell cooperation in the activation of antibody-forming cells (2–6), the synthesis and nature of products that can be released from such cells (7–9), and we have begun to learn something about the nature of mediators of cell-mediated immune responses (10,-11). We also have become increasingly aware of the importance of genetic and physiological factors that can influence the magnitude of immune responses (12,13). Yet, until recently there remained a paucity of information regarding the nature of molecular events that are responsible for the activation of immunocompetent cells and for the regulation of the magnitude of their response. While adjuvant effects and tolerogenic effects have been familiar and widely investigated phenomena for a long time and are known to involve the same cells (14), we have only just begun to understand some of the molecular events and cellular factors that appear to be critically involved in regulating the intensity of immune responses in general, and the functions of specific cell populations in particular (e.g., those responsible for antibody formation versus those involved in cell-mediated immunity).

Our own contribution to this subject has been based on attempts to elucidate basic mechanisms of inter- and intracellular events in immune responses by studying the effects of chemically well-defined modifiers of immune responses. Our overall objective has been the identification of normal regulatory factors controlling the activation and performance of cells involved in immune responses, and the utilization of this knowledge for a more effective manipulation of such responses.

*Compiled by Dr. Otto Plescia from excerpts of Dr. Braun's recent writings.