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EDITED BY

HENRY G. KUNKEL FRANK J. DIXON

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PREFACE

Progress in the field of immunology continues at an ever-increasing rate and at every level of investigation. The once mystifying maneuvers of DNA as a prelude to antibody formation and the manipulation of RNA in the course of carrying out orders from the immunologic genome are now reasonably well understood. No longer do we need to be primarily concerned with the basis of antibody diversity nor with the mechanisms of translating genetic information into antibody molecules. The complicated events underlying the manifestations of immunologic diseases are becoming better understood in terms of the cell types involved, their regulation provided largely by products of immunocytes and their effector mechanisms. The complex interrelationship between a host and a partially incompatible graft in the form of either a conceptus or a neoplasm is also being elucidated. The most effective defense of a fetus against an immunologically sensitized mother appears to be conducted by fetal suppressor T cells, which fight their battle in the trenches of the placenta. As we learn more about the nature of antitumor immune responses and the reasons for their relative ineffectiveness, possibly strategies may be devised that can influence the outcome of the host–tumor struggle. These are the subjects addressed in this volume, and they represent exciting excerpts from the broad spectrum of immunologic research.

Drs. Roger Perlmutter, Leroy Hood, and associates have chosen the murine antibodies directed against phosphorylcholine as a model system for studying the generation of antibody diversity, a subject to which they have been major contributors. In the first article they review the various elements contributing to diversity including the combinatorial association of heavy and light chains and joining of germline gene segments, the variable joining within gene segments, the appending of additional nucleotides to the D segment, and finally the somatic hypermutation operating coordinately on all V, J, and D gene segments. Together these mechanisms can generate a diverse repertoire of similar but distinct antibody specificities from a single germline V gene. The operation of these different diversity producing events is considered in the general context of B cell maturation, placing both molecular and cellular events in perspective.

The role of posttranscriptional RNA processing in the regulation and differentiation of B lymphocytes is reviewed in the second article by Drs. John Rogers and Randolph Wall. Discovery of the membrane gene segment established the μ heavy chain gene as the first example of a complex transcriptional unit in chromosomal DNA. This unit pro-

duced two heavy chain μ mRNAs with different 3′ spliced structures coding for secreted and membrane bound forms. The authors, who were key movers in this development, predicted and later found a similar complex transcriptional unit responsible for secreted and membrane forms of all immunoglobulin heavy chains. The coexpression of IgM and IgD on the surfaces of early B cells was also found to involve a complex transcription unit encoding both μ and δ mRNAs. This transcription unit was developmentally regulated by the choice of multiple polyadenylation sites and by selective recognition and use of RNA splicing sites. Thus, posttranscriptional processing appears to be intimately involved in the changes in μ and δ expression by maturing B cells. Recent demonstration of similar mechanisms operating in species as different as yeast and rat would seem to establish the generality of posttranscriptional RNA processing in eukaryotic gene regulation.

Although the binding of IgE to basophils and mast cells has been recognized for some time, the association of IgE with lymphocytes, monocytes, and macrophages is a more recent discovery. In the third article, Dr. Hans Spiegelberg summarizes the available data on the structure and function of Fc receptors for IgE on various immunocytes. Not only is the chemical nature of receptors for IgE on immunocytes quite different from that on mast cells but the strength of binding to the former is several magnitudes lower. The function of IgE receptors on immunocytes is not entirely certain. However, the number of receptor positive cells, and probably receptors per cell, parallels the levels of extracellular IgE, suggesting that they are a part of the IgE response. On macrophages and monocytes, IgE receptors promote phagocytosis and killing of IgE coated targets and, in the presence of IgE complexes, induce release of phlogogens. On lymphocytes the role of IgE receptors is less clear, but there is some evidence for the hypothesis that receptor positive T cells may be involved in down regulating IgE synthesis by B cells.

One of the great challenges in the field of immunology is the development of means to enhance host antitumor immunity. In spite of a few promising but inconsistent leads, there is no generally successful antitumor immunostimulatory measure. One of the major difficulties in this field is our lack of precise knowledge of the immunologic host–tumor interaction during oncogenesis and tumor growth. In the fourth article Dr. Robert North proposes concomitant antitumor immunity, i.e., the development of transient, early T cell antitumor immunity that is soon negated by the generation of suppressor T cells, as a rational model for the analysis of natural tumor immunity and for the development of appropriate therapeutic manipulations. He presents convincing evidence for the existence of such an antitumor response

in mice and then proposes means of potentiating or facilitating it to achieve the elimination of established syngeneic tumors.

Several factors probably contribute to the persistence of a histoincompatible fetus during a long gestation period in an immunocompetent maternal host. However, since the mother clearly becomes sensitized to a variety of fetal histocompatibility antigens during pregnancy, and since maternal immunocompetence is not systemically suppressed, it seems likely that the mechanisms primarily responsible for fetal maintenance act locally at the placenta inhibiting the action of sensitized maternal lymphocytes. In the fifth article Drs. David Jacoby, Lars Olding, and Michael Oldstone review this field, focusing on the potent suppressor effects of fetal lymphocytes, a subject to which they have been leading contributors. Apparently fetal lymphocytes, via their suppression of maternal immune functions at the site of placentation, are the major protectors of the conceptus during gestation.

In addition to its long recognized role as a vasoactive amine producing symptoms of allergic disease, histamine is now considered, together with prostaglandins and beta-mimetic catecholamines (the autacoids), as a regulator of both immune and inflammatory events. In the final article Drs. Dennis Beer, Steven Matloff, and Ross Rocklin review this field that has largely developed within the past decade. Histamine can be derived not only via the interaction of antigen with specifically sensitized mast cells, as in IgE reactions, but also by stimulation of sensitized effector T cells to make histamine releasing factor, which may provide a source of histamine in the absence of IgE mediated responses. Once available, histamine may act to modulate the immune response by activation of either or both suppressor and contrasuppressor cells with the result depending on the ratio of these two cell types activated. The effects of histamine on inflammation can also be pro or anti. Its phlogogenic effects are achieved at least in part via T cells; these are stimulated to produce chemoattractant and migration inhibitory lymphokines that attract and hold lymphocytes and eosinophils at sites of inflammation. The antiinflammatory effects of histamine are achieved both by directly suppressing the action of cytotoxic T cells, natural killer cells, neutrophils, and eosinophils and indirectly via suppressor T cells. The latter may augment the production of prostaglandins by macrophages and monocytes, resulting in inhibition of effector T cells and thereby dampening cell-mediated immune reactions.

As always, the editor wishes to thank the authors, who have given generously of their time and effort, and the publisher, whose staff does much to ensure a volume of high quality.

FRANK J. DIXON

HENRY G. KUNKEL
(1916–1983)

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(1916–1983)

Henry Kunkel's untimely death has left a void in the field of immunology which will be felt in many ways. Among the people who will miss his advice and guidance most will be those of us involved with the *Advances in Immunology*, a series he coedited since 1967. As an editor, his ability to recognize the most significant movements in immunologic research, to identify those most expert in the area, and then to prevail upon them to write scholarly reviews was unexcelled. Much of the success enjoyed by this series is owed to his efforts. It is appropriate that in this volume of *Advances* we present a close and rather personal view of this remarkable man's scientific career, and Dr. Hans Müller-Eberhard, a long time associate and friend of Dr. Kunkel, has joined in its preparation.

To a large extent Henry Kunkel was a self-made immunologist and clinical investigator. He had no formal training in immunology or biochemistry, nor did he have any clinical specialty training. He started his career at the Rockefeller Institute for Medical Research in 1945 in the field of liver disease. After the untimely death of his laboratory chief, he continued these investigations for several years making fundamental contributions to the diagnosis, prognosis, and treatment of liver cirrhosis. His interest in γ-globulin, which was to continue to the end of his life, originated with the study of this disease. To acquire expertise in protein separation by electrophoresis and to prove himself worthy of appointment to senior rank at the Institute, he took a leave of absence and worked at the Biochemical Institute in Uppsala under Arne Tiselius. After a most successful year with Tiselius, Henry Kunkel was promoted to full Member of the Rockefeller Institute and was given a laboratory of his own at age 36.

Henry Kunkel's art of conducting science was to establish a fact by simple technology. His laboratory was austere, containing only the necessary basic equipment. The intellectual input was all that counted. He was exceedingly well read in the biomedical science literature and had a penetrating and critical mind. By association of seemingly unrelated facts and by informed intuition he was able to identify potential breakthroughs in immunology. In the first decade of his career as an immunologist, he showed that myeloma proteins are immunoglobulins, that 7 S and 19 S γ-globulins are related but immunologically and chemically distinct proteins, and that rheumatoid fac-

tor is an autoantibody to IgG. He discovered idiotypy of human antibodies and, in an interlude between phases of strict immunologic research, he described hemoglobin A_2 and its relationship to thalassemia. All these early advances were accomplished merely employing precipitin techniques and starch block electrophoresis and ultracentrifugation as the only high-technology tool.

Henry Kunkel was an ingenious mentor of his research trainees and associates. Particularly in the earlier years he set an example skillfully experimenting at the bench. He was gifted in inspiring his people through long and frequent discussions conducted individually. He was a proponent of training in the philosophy of research which, he felt, involved questions concerning discipline of thought, intellectual integrity, respect for the written word, and the ethics of research work itself. He was masterful in creating an atmosphere in the laboratory in which fellows were compelled to go forward to eventual success or hopelessly fall behind. Tension in the laboratory was high at times and the admonishing reprimand "they will beat you to it" was a hard experience for a beginner in research and meant longer hours at the bench and greater mental effort. For some it meant humiliation and anguish. But good work, the exciting results of a "key experiment" that would "advance the field significantly," were always met with a beaming face and eventually would lead to true recognition, respect, and often lasting friendship. Henry Kunkel trained many young physicians and scientists and he did so with a phenomenal success rate. It seems a fair estimate that at least twenty senior professors of leading medical schools and research institutions, among them one Nobel Laureate and four members of the National Academy of Sciences, trace back the beginnings of their careers to Henry Kunkel's laboratory.

Henry Kunkel wrote lucidly, often pondering for a considerable time over the precise formulation of a sentence. His numerous publications attest to his talent as an author of scientific prose. Yet his spoken word could be sketchy, even vague, as though he was expecting the other person to know what he was talking about or to read his mind. He was impatient with ignorance, especially in relation to publications from his own laboratory. He was indignant with "shoddy" work published in the literature since his own high standards of performance did not allow publication of work unless it was thoroughly substantiated and documented: "one of our finest traditions in science," he wrote, "concerns the sanctity of the written word and the special pride involved in the avoidance of error. We should preserve it at all costs."

Henry Kunkel became a formidable leader and pioneer in the investigation of immune complex and autoimmune diseases in man. His abiding interest in antibody structure, function, and genetics which led to the elucidation of much of what is known today in this field, was later extended to studies of B cell-associated immunoglobulins and recently to the T cell antigen receptor. In recognition of his many fundamental contributions to immunology and medicine he received numerous awards and honors. He held an endowed chair at the Rockefeller University, the Abby Rockefeller Mauze Professorship, and he had been president of two learned societies, the American Society for Clinical Investigation and the American Association of Immunologists. Yet neither the honors bestowed on him nor his natural dignity and high self-esteem prevented him, when the occasion arose, from joining his associates and friends in merry socializing. He delighted in playfully poking fun at them and being the target of their humorous attacks. Such situations revealed the engaging warmth and the humanness of his personality.

Henry Kunkel will be remembered as the gifted teacher and scientist he was, endowed with the drive and ability to be creative and to be productive throughout his life. He was dedicated to and excited by science. As he put it, "scientific inquiry is a sort of opiate that once experienced is not readily shaken off." Those who knew him well in the scientific community, his students, colleagues, and friends, will behold his memory with the admiration and deep affection they had for him.

HANS J. MÜLLER-EBERHARD
FRANK J. DIXON

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I. Introduction

The ability of higher vertebrates to mount an immune response to a seemingly infinite variety of distinct antigens has attracted the attention of biologists for decades. In particular, immunologists have struggled to explain the extraordinary diversity of antibody molecules. During the early part of this century, Landsteiner's classic analysis documented the exquisite specificity of immunoglobulins, which, for example, could clearly distinguish between identical chemical structures substituted at different positions on a phenol ring (Landsteiner, 1945). These early results prompted "instructionist" theories which viewed antigen as a template around which antibodies would fold.

Beginning around 1960, structural analysis of antibody polypeptides defined the kappa, lambda, and heavy chain families, and the sequence studies of Hilschmann and Craig (1965) and Putnam (reviewed in Putnam *et al.*, 1971) identified light chain variable (V) and constant (C) regions. Viewing these data, Dreyer and Bennett suggested with admirable foresight that antibody heavy and light chains are encoded by more than one gene, thus anticipating the noncontiguous nature of eukaryotic genes and the DNA rearrangements which are central to the formation of antibody coding regions (Dreyer and Bennett, 1965). More detailed structural analysis revealed that the amino terminal variable regions of both heavy and light chains contain three short segments of hypervariability (Wu and Kabat, 1970; Capra and Kehoe, 1974). These hypervariable regions were shown by X-ray crystallography to comprise the antibody combining site (Padlan *et al.*, 1973; Amzel *et al.*, 1974), whereas the remaining portions of the variable region are relatively invariant in structure and hence are called "framework" regions.

In the early 1970s the problem of antibody diversity was approached at the nucleic acid level. Hozumi and Tonegawa (1976), using cDNA probes for murine kappa light chains, were the first to show that the constant and variable region-encoding segments of antibody genes are separated by intervening DNA in the germline but are more closely juxtaposed during B cell differentiation. Four separate coding regions, leader (L), V, J, and C, for lambda genes were identified (Brack *et al.*, 1978) and a similar analysis was carried out on