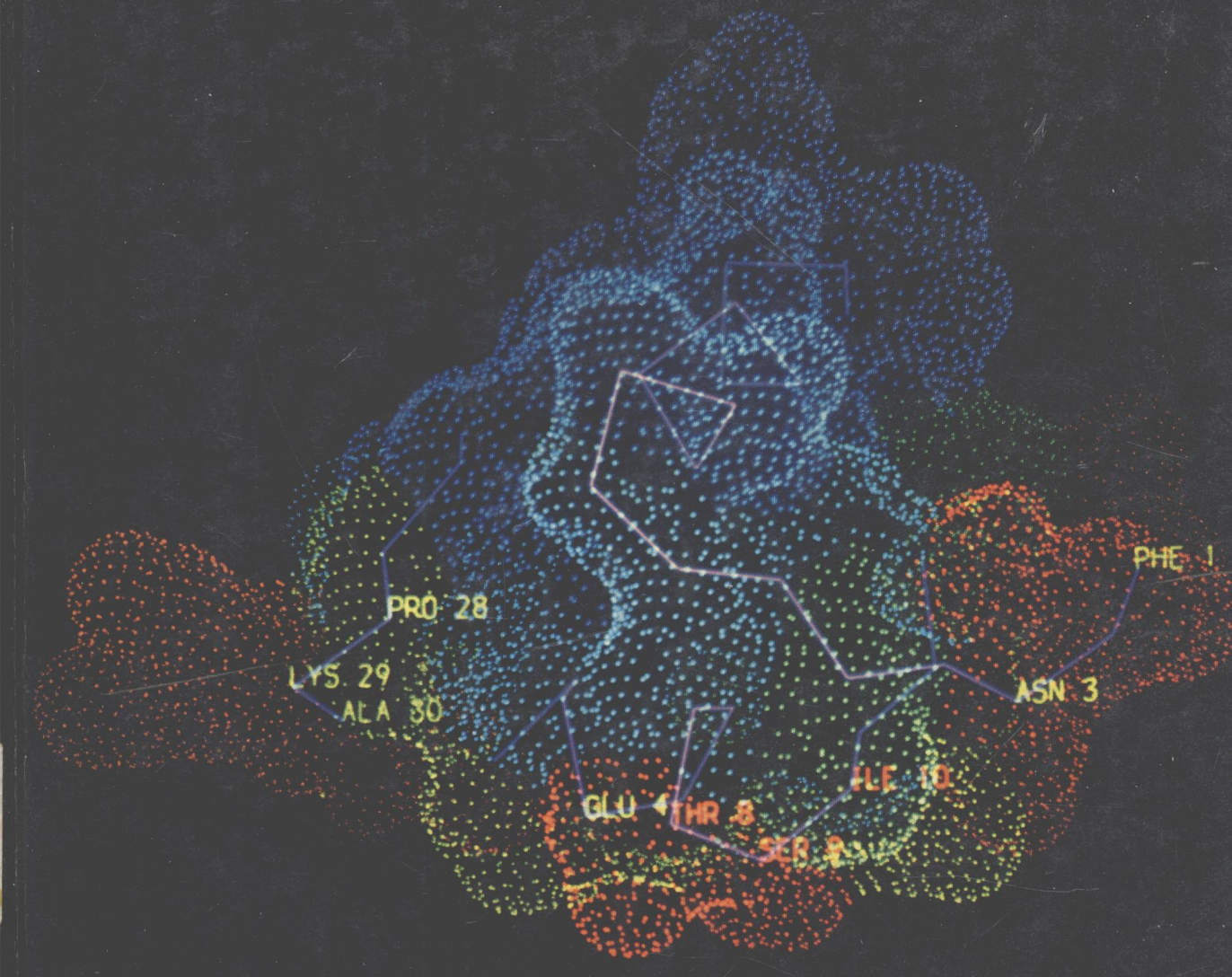
IMMUNOLOGY: A SYNTHESIS

EDWARD S. GOLUB



IMMUNOLOGY
A SYNTHESIS

EDWARD S. GOLUB
DIRECTOR OF RESEARCH
ORTHO PHARMACEUTICAL

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THE COVER

Computer graphic view of insulin showing that antigenic determinants cluster at highly flexible regions. The alpha carbon backbone is shown with purple lines. The molecular surface is indicated with dots, color-coded from most mobile to most rigid in the order red, yellow, green, cyan, blue. Residues forming antigenic determinants are labeled in pink (contiguous) and yellow (discontiguous) and can be seen to correspond with the more mobile regions (see pages 28 and 29). [Image created by John A. Tainer and Elizabeth D. Getzoff, Research Institute of Scripps Clinic]

PART-OPENING ELECTRON MICROGRAPHS

Part One, p. 15: Antibody–hapten complex (purified rabbit anti–2,4-dinitrophenyl antibody and a bivalent hapten). [From R. C. Valentine and N. M. Green (1967), *J. Mol. Biol.* 27, 615]

Part Two, p. 155: A resting lymphocyte, probably a T cell, ×21,840. [Courtesy of D. Zucker-Franklin, New York University Medical Center]

Part Three, p. 437: Immune complexes, seen as electron-dense, hump-shaped deposits in the upper third of the photo, along a capillary wall in a glomerulus following streptococcal glomerulonephritis (×17,250). [Courtesy of M. N. Yum, Indiana University Medical Center]

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To the two most important women in my life,
My MOTHER *and my* WIFE, CONSTANCE,
and to the memory of two important men in my life,
My FATHER *and my* FRIEND, GOOCH

Preface

This book is an extension of both my earlier book, *The Cellular Basis of the Immune Response,* and my personality. My aim is to convey to the nonimmunologist the complexity, logic, and above all the beauty of the immune system. The purpose of any textbook in the sciences should also be to teach the mode of thinking of the discipline and to convey the excitement that the participants in the field feel as they attempt to uncover the beauty, logic, and complexity. As I did in *The Cellular Basis,* and as I do in all of my teaching, I have attempted to define the problems of the field and then to lead the student through the reasoning that led to the solution. This means that it will be very difficult to go through this book with a Hi-liter marking pen to cram for a machine-scored exam. This method of teaching requires active participation because, God knows, the doing of science is not a passive activity. As I mention in the Note to the Reader, I have made every attempt to help organize the reader's thoughts by breaking the book into manageable sections, so little energy has to be expended in trying to figure out where one is.

This book, though covering a much wider range of material than *The Cellular Basis,* like its predecessor is not a compendium of facts. It is meant to prepare the reader to read the immunology literature so that he/she can follow the continuing progress in the field. It most certainly is not meant to be used only by immunologists. The mode of thought that immunologists use is not unique. Each discipline solves its problems with different tools, but the practice is the same: defining the problem, designing the experiment, and interpreting the results in order to ask the next question.

In *Chance and Necessity,* Jacques Monod says that anyone who does not use an analytic or reductionist view to approach systems as complex as living beings "is doomed to fail in (the) attempt to reduce the properties of a very complex organism to the 'sum' of the properties of its parts." I have taken a reductionist view of the teaching of immunology, attempting to break the subject down into concepts, then describing the concepts in such a way that the whole picture emerges. When a complex subject is divided into its component parts, the viewpoint of

the author always comes through. With this come all of the ambiguities, redundancies, and deficiencies of that viewpoint. A case in point is quoted by Borges in *Other Inquisitions 1937–1952*:

> These ambiguities, redundancies, and deficiencies recall those attributed by Dr. Franz Kuhn to a certain Chinese encyclopedia entitled *Celestial Emporium of Benevolent Knowledge*. On those remote pages it is written that animals are divided into (a) those that belong to the Emperor, (b) embalmed ones, (c) those that are trained, (d) suckling pigs, (e) mermaids, (f) fabulous ones, (g) stray dogs, (h) those that are included in this classification, (i) those that tremble as if they were mad, (j) innumerable ones, (k) those drawn with a very fine camel's brush, (l) others, (m) those that have just broken a flower vase, (n) those that resemble flies at a distance.

Because this book is not a compendium of facts I have ordered the subject of immunology in what I think is the clearest sequence for approaching the major questions of immunology. Others, like the author of the *Celestial Emporium*, will have other viewpoints.

Contrary to the generally held belief, I am not an expert in all aspects of immunology. My own work has been in cell interactions and surface molecules and is currently in the differentiation of stem cells. I needed help from many, many people to attempt this expanded book. The following are some of the people who, over the last three years, have been of great help to me in preparing this book. I have relentlessly and sometimes cruelly picked their brains to find their views on a field, get preprints, have drafts read, and find my way out of an occasional morass. I apologize to the many people whose names I have neglected to include in this list; if the book stinks, you will be relieved not to have been associated with it.

Joe Albright, David Asai, Don Bailey, Dave Benjamin, Eli Benjamini, Jay Berzofsky, John Cambier, Henry Claman, Carol Cowing, Harvey Cantor, Dick Dutton, Marc Feldman, Doug Green, Gene Goldwasser, Allison Hall, Lee Hood, Richard Hodes, Chris Henney, Niels Jerne, Jack Johnson, Dave Katz, John Kappler, Rich Lerner, Av Mitchison, Pippa Marack, John Najarian, Judith Owen, Martin Raff, Yvonne Rosenberg, Osias Stutman, Eli Sercarz, Liz Simpson, Kendall Smith, George Snell, Susie Swain, Al Singer, Don Shreffler, Ed Simon, Irwin Tessman, Leon Weiss, Dorothea Zucker-Franklin, Maurizio Zanetti.

I am especially indebted to Larry Draper and Lee Metcalf for their thorough critical readings of the entire manuscript, which caught so many inelegancies and stupidities. In the last book I blamed any faults on other people; Larry and Lee must be excused from any blame because I did not always take their advice. As usual, the staff of the Jackson

Laboratory in Bar Harbor were wonderfully helpful, as were the librarians at Case Western Reserve University Medical Schools.

This book was harder for me to write than *The Cellular Basis of the Immune Response,* partly because the field has changed, and partly because I included so much more of immunology in this book. But to a large degree I must admit the difficulty was because both immunology and I have entered middle age and we both are more difficult to deal with than we used to be. Others had to bear the burden of this condition and, while the reader may not be interested in my problems, I feel honor-bound to tell those who suffered that I am aware of their kindness, devotion, and anger:

The expanded crew at Sinauer Associates, who have had to deal with a bigger book and a more crotchety author (especially Joe Vesely, who I finally pushed to the edge of not smiling), and, of course, that sure-handed shortstop and trusted friend, Andy Sinauer, who charted the course of this adventure and only appeared to be coming close to abandoning ship. I hope the case of scotch will put me back in the good graces of this beleaguered group.

And, of course, my family: my wife, Constance, who put aside the galley proofs of her own first book and the manuscript of her second to listen to my woes and never hesitated to comfort, humor, or correct egregious solecisms; my son Jon, who had the good sense to leave home during the ordeal; and my son Mark, who wished he could have followed his brother but, finding himself stuck, was a constant source of joy and occasional editorial help; my mother, who naturally thinks that her genius son deserves all of this devotion; and, finally, Terasita Pagan, who ran the lab and delivered Deborita as if all were normal.

But even with this difficulty, in retrospect it has been a joy to do this book, because it has given me a chance to rethink the field I have worked in all my scientific life and love so much. Twenty years ago neither I nor any of my contemporaries could have predicted the wonderous twists and turns the field would take, and I don't think that many of us could have guessed the real beauty of the immune system that has been revealed. If the reader comes away from this book feeling half the wonder and joy about the immune system that those of us who have been participants feel, then my little problems in writing the book will seem as nothing.

E. S. GOLUB

A Note to the Reader

> I don't know what's the matter with people:
> they don't learn by understanding; they learn by rote
> or something. Their knowledge is so fragile.
>
> —Richard Feynman, *Surely You're Joking, Mr. Feynman,* p. 23.

The reader of this book should be aware at the outset that I feel very strongly that the way to learn science is not to learn a bunch of facts. Science is a process of solving problems to figure out how the world works. And the way to really learn science so that the knowledge is not fragile is to immerse oneself in the process. I have tried to fashion this book according to that passion. Certainly, one needs to know facts in science. But I strongly believe that we need them only to carry the process further. Because our understanding of the world changes, every scientist gets only a temporary view of what we think the world is like. To master the facts of the current view of the world is, to me, a rather futile pastime if one is not also gaining the ability to follow future changes in a given field.

As much as possible I have tried to organize immunology along *conceptual* lines. The pattern of this approach will become obvious as the reader moves through the text. In order to maintain the continuity of thought, I have included Methods Boxes and Information Boxes along the way. The Methods Boxes will give the reader who needs it an understanding of the method being used in an experiment described in the text. The Information Boxes are for reference if the reader needs or wants more facts.

I have tried to organize the book into conceptual blocks, which are clearly marked by typography. The plan is that every reader should know where he/she is in the unfolding saga. For as much of the material as I could I have begun by stating the problem as it was viewed in the last decade, which for immunologists is the distant past, and then following the path of experiments that have lead us to the present view. But as I said, the present view is temporary, and my hope is that by following the flow of the ideas and experiments the student will be able to understand the next phase as it unfolds.

A NOTE TO THE READER

Of course, one can choose to read only the "bottom line" and buy the next edition of the book to see how things have developed. That will please me, as I use the royalties to pay my sons' college tuitions. It will not, however, please the people who pay the tuition of students who use this book in a course. If you won't learn the process for me, do it for them!

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