Immunity, Vol. 11, 649–651, December, 1999, Copyright ©1999 by Cell Press

Immunology at 2000

Editorial

The last days of a year or century or millennium are artificial barriers in time, but nonetheless to recognize these points in time has some utility. They allow us to pause, look back, and reappraise what we have done and where we now are. As individual scientists, such reappraisals are perhaps not done with optimal frequency. As a group or a community, such reappraisals are uncommon and done even less to orient the field into a forward direction. Scientific progress tends neither to be organized nor well planned. It may pay little attention to the historically important events that moved a field forward or to the natural forces that shaped the field, but rather preys upon the immediate menu of findings, new technologies, and fashionable lines of inquiry. We now pause, albeit briefly, as year's end approaches and our tenure as editors of *Immunity* terminates, to ponder what the second century of immunological research has accomplished. Where are we? Where are we headed? What are our expectations?

That day in July of 1798, when Edward Jenner inoculated James Phipps with vaccinia virus derived from a cow named Blossom, represents the start of immunology as a discipline. Following the extraordinary success of cowpox vaccination in controlling smallpox, several decades passed without any real understanding of immunological reactions. The analysis and understanding of these reactions arose from the formulation of the germ theory of disease championed by Pasteur and Koch, the discovery of neutralizing factors for toxins in antisera—the epochal results of Von Boehring and Kitasato—and our early comprehension of cells and tissues and diseases, brought about in particular by the emergence of the cell theory. The first century of immunology ended circa 1900 with the two giants who profoundly influenced the analysis of immunological phenomena: Paul Ehrlich and Elie Metchnikoff. Ehrlich's renowned Croonian lecture to the Royal Society in 1900, during which he first stated the side chain theory, represents creative thinking at its best. Remarkably, at this time practically nothing was known of immunological specificity nor of the cells that conveyed it. Metchnikoff's postulation on the role of phagocytes and phagocytosis was likewise a landmark in presaging what we now call innate immunity—the old reticulo-endothelial system, actually not a bad term at all. These two extraordinary scientists defined how the immune system operated within the limits of their knowledge and created a vision of the future beyond the knowledge at their disposal.

But again, as with Jenner's findings, a period of time had to pass for their vision to come to the forefront of immunological research. Indeed, up to the late 1960s, immunological research focused on the immediately obvious and the technically feasible: the analysis of serum antibodies. We learned about the ways to elicit antibodies and their role and use in combating infections. (The first Nobel Prize in Medicine was awarded to von Boehring for his findings on serotherapy.) The different technologies to appraise and measure the interactions between antigens and antibodies were developed so that the fine chemical specificity of the interactions could be understood. Much was learned from the identification of different chemical forms of antigens and from the concepts of haptens and carriers. Haptens allowed for the correct measurements of antibody affinity, which led to the recognition of affinity maturation during the immune response. Biologically, we came to appraise the function of antibodies in opsonization, in activation of serum complement, and in immune complex–type diseases and clinical allergies. The culmination of all these years was the elucidation of the beautiful structure of an antibody molecule with its component chains and its unique functional domains.

It is not that cellular reactions were completely ignored during this time. But progress here was slow and the center of the field was elsewhere, i.e., with the analysis of the "humoral response." It is startling to realize that experimental proof that lymphocytes convey the specificity of immune responses has been known for about 30 years. Around late 1965, the second epoch of immunological research ended as the emphasis in the discipline abruptly changed with an increased awareness of the phenomena reported by Ehrlich and Metchnikoff, that is to say, the analysis of lymphocytes and the RES. From 1970, progress has been notable and revolutionary, as modern cellular and molecular biology and genetics enter this field, which has now exploded with extraordinary dynamism and has attracted some of the best minds in biology. Now approaches could be taken to understand the cellular basis of an immune response: the lymphocyte is the most studied and best known cell in biology. The advances of the past two decades in particular are nothing short of extraordinary, spilling beyond the confines of immunology per se. Few biological disciplines have had such an acute period of accomplishments. One can well argue that the discipline moved so fast because we were firmly planted "on the shoulders of giants." Indeed, it had taken close to one century to get ready, but in barely three decades:

(1) Lymphocytes are defined as providing the cellular basis for immunological specificity.

(2) The two major subsets of lymphocytes are identified.

(3) The clonal nature of lymphocyte recognition is determined.

(4) The lymphocytes' receptors for antigen are discovered and cloned.

(5) Monoclonal antibodies are developed, and with this accomplishment comes not only a fundamental understanding of B cell biology, but also the widespread use of homogeneous antibody finds enormous practical application.

(6) The molecular basis of diversity is resolved with the discovery of gene rearrangements.

(7) T cell recognition of antigen is deciphered, and the MHC, discovered prior to this time, is now placed in the correct perspective of physiological interactions.

(8) Antigenicity is placed in the framework of antigen processing, presentation, and peptide-binding to MHC,

and the unique structure of MHC molecules is elucidated.

(9) The role of the thymus in T cell development and in the selection of T cells is discovered and with it comes an understanding of immunological tolerance, discovered years earlier.

(10) A whole family of new molecules, the cytokines, are discovered—most are purified and their genes cloned. Cytokines are shown to orchestrate cellular communication, to promote and/or regulate most immunological reactions, and to play key roles in promoting host defense and immunopathologic reactions.

(11) The mode of cell-to-cell communication is now examined at the fine molecular level as identification is made of a whole set of membrane proteins that mediate different expressions of cellular interactions; indeed, the molecular mechanisms underlying intracellular signaling within cells of the immune system starts to be understood.

(12) The era of clinical immunology is launched: many clinical diseases are identified to be caused by abnormal immunological reactions, and the molecular basis of many of them is resolved; autoimmunities are acknowledged as important immunologically based diseases; the relationship among microbes, their virulence, and pathogenic components of the host begins to be understood; and organ transplantation becomes a strong component of modern medicine.

The third century of immunology research starts with the decade of the 1970s, which was crucial, but, now viewed in hindsight, mired with problems. Many good questions were asked, but the time was not ripe to answer all of them, and a few wrong roads were taken. This confusing decade nevertheless had to be endured as the new cellular approaches were being created. Still, very notable findings came out of this period, such as the realization that surface immunoglobulin was indeed the B cell receptor for antigen and the landmark studies on the role of the MHC and MHC restriction in T cell responses, both of which poised the research, up to this time. But by the 1980s, we were well on track, with technology and biology finely integrated so that questions could now be asked that were never even thought of just 10–20 years before. It was at this time that immunological phenomena began to be explained on a mechanistic molecular basis. There was no longer a split between "cellular" and "molecular" immunologists. Immunology at the close of the century is on a path-finding course from the outside of the cell into the nucleus. It has gone so fast that we have yet to stop and integrate all the information brought about by gene knockouts, transgenics, the discovery of new genes, and their manipulations.

So what then are our predictions of what is to come? Although this may indeed be a futile exercise that will be entirely negated by the next high impact papers, we present here some of our thoughts.

We still need to know much more about how the immune response starts and how it stops. The symbiosis between the innate and the adaptive limbs of the immune response remains a fertile area of research. Specifically, we need to determine how a nonclonal innate system of recognition (i.e., the RES) operates and how it functions together with the clonal adaptive system represented best by the lymphocyte; that is, we need to define the interface between the worlds of Metchnikoff and Ehrlich. This interface has to be understood not only at the usual reductionist level of identification of the role of membrane proteins and cytokines, but in the framework of the whole organism. We still need to know the many components involved in the reorganization of lymphoid tissue as antigen enters them and what may be the many controlling events taking place. We have good readouts of positive and negative interactions, but our sense is that there are very big gaps here in our level of understanding. The same pertains to the end of the response.

Indeed, we need to define the transcriptional programs that lead to the development of activated or differentiated effector cells of the immune system. This includes not only defining the tissue- and cell-specific transcription factors that are involved in the process, but also in identifying the target genes of these transactivating factors. Clearly, this is an area that has developed during the last years of this century and will be an extremely active area of research for many years to come. For this purpose we believe that genomics will play a key role in driving immunologic research in the twenty-first century, but not randomly. Rather, the future of immunologic genomics rests in our ability to integrate this technology into the biologic framework of our discipline.

Finally, we clearly need to bring more of the basic principals we are learning about the immune system into the arena of human diseases. We still do not know how to effectively tolerize to a particular antigen or to allogeneic MHC–peptide complexes. Or, ironically, for that matter, the principles of vaccination are far from developed. We have made great strides in developing immunologically based therapies against many of the great infectious diseases of our time. However, we are still losing the battle against parasites, certain viruses, and intracellular bacteria, which have found ingenious mechanisms to circumvent the immune response, often by capturing a piece of the host defense system and adapting it for its own use. This problem is particularly relevant when applied to cancer. Although we now are aware of a large number of proinflammatory and immunomodulatory cytokines and their receptors, we are still a long way off from using this knowledge therapeutically. The challenge will be to identify specific patterns of cytokines that drive a particular response and then find ways of eliciting or administering these cytokine arrays to change the course of a human disease, particularly autoimmune diseases such as arthritis, SLE, and IDDM. Perhaps in the not-so-distant future it will be possible to circumvent the need for administering cytokines altogether when the molecular pathways of cytokine signal transduction are fully worked out and the specific gene targets of a particular cytokine can be turned on or off iatrogenically.

The four of us were fortunate to enter the field during the last period (albeit at different times!) and to participate in some of the events that have taken place. Jan Klein said, when admiring a painting by Gaugin and then comparing a work of art to a work of a scientist, that we all contribute by placing chips in the vast mosaic of science. Some of us may be fortunate to place a piece

that fits well and is prominent, while others may place smaller pieces and, unfortunately, some may not fit well and may even fall off. But the game was great fun to play, since the mosaic has much beauty to it and to fill in the pieces is always a challenge. Indeed, this is the challenge to all of us, to recognize the vastness and the beauty of the immunologic mosaic and to make sure that all the chips, including the central ones, all fit well.

In a short while we will be ending our tenure as editors of this journal. The journal was started because of the vision of Benjamin Lewin that immunology was in a position to have a major journal that would contain unique and seminal papers. The Harvard editors who started *Immunity* (Abul Abbas, Frederick Alt, Laurie Glimcher, and Hidde Ploegh) made a superb effort in setting the tone of *Immunity*, and indeed they deserve the major credit for developing it. We followed through on the firm base that was set up by them. We have many to thank for the help that we were given. Benjamin Lewin was always available to provide advice, and the staff at Cell Press was always devoted to the journal and to making sure that the authors were well served. So was our own staff here at our Department of Pathology and the Center for Immunology. The review editors, first Charles Janeway and later Alfred Singer, also provided much help. The journal would not be a success were it not for the help of our many colleagues who served as reviewers—they have come from all over the world, and we thank them all for their help. We received much help from our colleagues at Washington University, who always went out of their way to advise us on papers and to give this advice in a very expeditious manner. But, of course, the journal depends on the investigators who send us their best work. We believe to have maintained the trust and confidence of our fellow scientists everywhere. We have tried to be fair, to base ourselves entirely on the merits of the submitted paper, and to maintain a balance among the areas that comprise immunobiology. Our thanks to all and our best wishes to the third editorial board.

Paul M. Allen, Kenneth M. Murphy,
Robert D. Schreiber, and Emil R. Unanue
Pathology Department
Washington University School of Medicine
St. Louis, Missouri 63110