nature immunology volume 3 no 9 september 2002

Natural evolution

Areas of inquiry initially arise because major holes in our understanding of the world act as obstacles to progress, whether it be intellectual or practical. If the questions pursued in the field are constantly changing, though, can one truly define a field of inquiry? From its inception, immunology has been driven by a few large issues of the day. When Jenner at the end of the 18th century (and later Ehrlich) pursued his interest in gaining protection against infectious agents, he was unaware that he was founding a new discipline. His pioneering work was initiated from a very practical need—to lower the rates of death and morbidity caused by some common pathogens. Pasteur and Koch showed more intellectual interest in isolating and understanding the organisms that cause disease. Metchnikoff made observations and proposed hypotheses that shed light on different areas entirely; now, however, all these areas—vaccination, antibodies, microbial pathogenesis, innate immunity and cellular immunology—fit easily under the immunology umbrella.

The field was shifting: those initial investigators would not have recognized the conundrums of tumor survival and transplantation in the first half of the 20th century as having any bearing on their own pursuits. And yet, this was a direction in which immunology had moved. Observations in transplantation slowly added weight to the realization that specific cellular responses were important in protecting us from foreign bodies. The study of transplants, and the immune cells involved, converged with data that implied a role for immune cells in delayed-type hypersensitivity. This eventually led to the elegant demonstration by Miller in the early 1960s that cells in the thymus were critical for immune responses.

In the late 1940s and early 1950s, pursuit of the cause of graft rejection led to the hypothesis of immune tolerance; the exquisite specificity of immune responses led to a theory of clonal selection. Seeded in these lines of investigation were questions that occupied the field for the next couple of decades and raised the profile and excitement in immunology to new levels, as immunologists realized the dimensions of the debate. Distinguishing self from nonself and determining how the immune response could respond to a diversity of antigens with such specificity were fertile areas of inquiry. Zinkernagel and Doherty's experiments establishing that antigen was recognized in the context of self and Tonegawa and Hozumi's discovery that immunoglobulin genes undergo recombination pointed the way toward resolution of these issues.

Time moves on and fields mature. But for every question answered, at least two seem to spring in its place. Problems that consume early investigators are solved as technology allows and knowledge accumulates—both within the field and beyond. Insightful findings in other areas have always influenced immunology. For example, investigators were quick to respond in the 1980s and 1990s to evidence that cells perceive extracellular signals through precise pathways. Knowing the proteins and genes for the T cell receptor, and seeing the possibilities for understanding T cell activation, precipitated a reinvigoration of intracellular biochemistry. Intensive studies soon revealed the role of intracellular proteins in the transduction of signals initiating from antigen, adhesion and cytokine receptors on immune cells of all types. Vast numbers of immunologists joined their molecular biology brethren (who for years had been piecing together the genetic regulation of immunity) in pursuit of a molecular understanding of how the immune system operates, and how its cellular components live and die.

As the pathways for cellular activation become less opaque, the tide is changing again. In the past five years or so immunology has begun to turn from the ultimate minutiae of molecular mechanism to a rekindled interest in the bigger immunologic universe. Concurrently, biology as a whole has been pursuing a more holistic approach with its multiple genome projects and acceptance of "big science". How can molecular understandings eventually predict what a given individual's reaction would be to a particular antigen, or better yet, pathogen? Will enumeration of the molecules involved in a phenomenon such as tolerance soon lead to manipulation, at will, of the intensity or type of immune response? Turning off and dampening down immune responses is an area that hasn't yielded its secrets easily. The flip side of this issue—that of breaking established tolerance or changing conditions that discourage effective responsiveness—has also been troublesome. Will these issues turn out to be related in some crucial fashion to another critical area, that of how innate immunity and different tissue environments alert the adaptive response to generate the appropriate responses?

As those who identify themselves as immunologists (and those who don't yet realize that they, indeed, are) move fluidly from area to area and creatively push the goalposts of the field, immunology itself cannot help but become richer for it. And *Nature Immunology* anticipates being the venue for immunology in the widest use of the term—bringing to its readers the finest from the newest edges of the field, maybe even before it is generally accepted that it is immunology.