Immunology near the millennium

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TRIBUTE TO ZELIG (ZECK) H. LIEBERMAN, MD

Zeck Lieberman is a consummate physician. Every day for over 40 years he has practiced the art and science of medicine and surgery as well as anyone I’ve ever seen. He exemplifies the importance of hard work, close observation, ongoing education, and a practical approach to the issues at hand. His wit, humor, warmth, compassion, and humane concern for patients and colleagues serve as an inspiration to us all.

Zeck has been a major contributor to the growth and development of the Sammons Cancer Center and oncology activities at Baylor at all levels. Armed with hand-drawn charts and diagrams, he explains his views and then asks if we agree. Usually, we do!

This 95-year-old institution—through its visionary administration, outstanding medical staff, and generous community support—has become a hospital recognized for service to patients and devotion to excellence. It is dedicated to patient care, education, and research. Most acknowledge that future progress in medicine comes about only through carefully conducted research. The decision to select immunology as the discipline that would contribute most to the strong clinical programs here in the coming years was made after much thoughtful discussion. It is particularly fitting that the building in which many of these exciting scientific activities will be carried out has been named for one of our most esteemed clinicians.

IMMUNOLOGY AND MEDICAL SCIENCE

The year 1998 marks the 200th anniversary of the report by Edward Jenner, an English country physician, of the first successful prevention of smallpox by the procedure known as vaccination (1–4). This spectacular advance introduced the concept of immunity. We all know that other infectious diseases can be prevented by inoculation of material into an individual, which provokes an immune response that subsequently prevents that person from contracting the disease. The seminal contributions of Louis Pasteur in the late nineteenth century showing that live, attenuated vaccines could be useful in the prevention of anthrax and rabies are well known (5). During our own lifetimes, we’ve seen the success of this approach dramatically demonstrated again in another scourge of mankind, polio. The World Health Organization declared that smallpox had been eradicated from this planet in 1979, and we seem close to achieving the same welcome result with respect to polio.

Almroth Wright was a well-known British immunologist who became director of the inoculation department at St. Mary’s Hospital in London at the turn of the century. He developed typhoid vaccine and described opsonins—substances (antibodies) in the blood...
that promote phagocytosis of infectious organisms, particularly after the subject had prior contact with these organisms and had acquired some immunity. Wright was a strong advocate of vaccine therapy and predicted that “the physician of the future will be an immunisator” (6). Bernard Shaw knew Wright well and used him as the model for Sir Colenso Ridgeon in Shaw’s play The Doctor’s Dilemma (7). In the play, one of Ridgeon’s physician colleagues utters the following words: “There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes. Drugs are a delusion.”

Despite triumphs in the prevention of some infectious diseases, immunology remained largely a laboratory science until the middle of this century. Blood transfusion was the outstanding exception. A real breakthrough came in 1901 when Karl Landsteiner, a chemist, identified the major human blood groups, a discovery for which he later received the Nobel Prize (8, 9). Landsteiner’s monumental contribution was crucial in providing the scientific basis for making blood transfusion a successful therapeutic modality and in launching the science of immunogenetics. Since 1950, an explosion in knowledge has made it clear that the immune system has much broader importance in health and disease. The field shifted from a chemical to a biological orientation. Two key conceptual advances fueled this explosion. The first was that cells known as lymphocytes are the principal elements of the immune apparatus, and these cells comprise a vast communication and recognition network throughout the body of every one of us (10). The second was that this cellular network is able to distinguish, with incredible accuracy, “self from nonself” (11, 12). Macfarlane Burnet and Peter Medawar received the Nobel Prize in 1960 for the latter concept, known as acquired immunological tolerance. Ordinarily, the immune system does not react to an individual’s own tissue but literally erupts into a “commotion” in the blood and other sites when it detects something foreign to that individual (13).

The dual nature of the immune system was apparent early on. Cellular and humoral theories of immunity were promulgated, and each had devoted adherents. Metchnikoff stressed the importance of white blood cells or phagocytes (14, 15). Ehrlich became associated with the humoral (antibody) concept largely because of his side-chain theory, in some respects a surprisingly similar precursor of Burnet’s clonal selection hypothesis a half century later (16, 17). Metchnikoff and Ehrlich shared the Nobel Prize in 1908. Almroth Wright’s opsonins appeared to bridge the cellular and humoral approaches. In Shaw’s words, “the white corpuscles or phagocytes which attack and devour disease germs for us do their work only when we butter the disease germs appetizingly for them with a natural sauce which Sir Almroth named opsonins . . .”(3, 7, 18).

Years later, the bursa of Fabricius in chickens and the thymus gland in mammals were shown to be sites where immature lymphoid cells acquired the capacity to function in humoral and cellular limbs of the immune response. B (bursal-derived) and T (thymus-derived) lymphocytes became the recognized elements in antibody production and cell-mediated immunity, respectively. Many lymphocyte subpopulations were later delineated, including helper and suppressor/cytotoxic T cells. Communication among the different subsets was shown to be facilitated through direct contact and by a number of secreted molecules termed cytokines (or interleukins). Cellular immunity was demonstrated to mediate delayed-type (tuberculin) hypersensitivity, allograft rejection, and graft-vs-host disease in addition to its “helper” function in antibody synthesis.
The demonstration in the 1940s by Medawar, a zoologist, that allograft rejection was immunologically mediated was a crucial milestone that launched modern transplantation immunobiology (19-21). Subsequent identification of histocompatibility genes, i.e., human leukocyte antigens (HLA), laid the foundation for allotransplantation of solid organs (e.g., kidney, liver, heart) and bone marrow. Later, the demonstration that major histocompatibility antigens play a critical role in specific cellular immune responsiveness through major histocompatibility gene complex (MHC) restriction was of paramount importance in understanding the complexities involved in immunity (21-22).

The multichain polypeptide nature of antibody molecules, now called immunoglobulins, was elucidated by Porter and Edelman in 1959 and led to amino acid sequencing and delineation of their antigen-binding sites. This Nobel prize–winning work was aided immeasurably by the availability of large amounts of homogeneous immunoglobulins from patients and mice with myeloma. The Cold Spring Harbor Symposium on “antibodies” in 1967 signaled the arrival and acceptance of immunology as a respected “core” science by colleagues in molecular biology and genetics (23). James Watson and Francis Crick, the codiscoverers of DNA structure, participated in this meeting. It was both disappointing and reassuring that neither member of the team making the most important scientific discovery of the twentieth century could explain the mechanism of antibody diversity better than anyone else. In addition, there was much excitement at Cold Spring Harbor about Watson’s forthcoming publication of his controversial memoir, The Double Helix, which appeared the following year (24). It was a thrill for me, a 29-year-old clinical associate from the National Institutes of Health, to participate in this historic meeting (25). The riddle of antibody diversity was not solved until a decade later when Tonegawa and others elucidated the elegant and complex somatic recombination and hypermutation mechanisms in immunoglobulins, which permit their exquisite specificity, on demand, for millions of potential antigens (22).

The hybridoma technique developed by Köhler and Milstein in 1975 revolutionized immunology (13). These investigators were awarded the Nobel prize for showing that antibody-producing cells of virtually any desired specificity could be fused with a myeloma cell line, the result being unlimited amounts of homogeneous (monoclonal) antibodies carrying that specificity. Such monoclonal antibodies are now employed as defined reagents by immunologists and a variety of other scientific investigators throughout the world. Hybridoma technology also has proved to be of great use in clinical diagnostic immunology. Monoclonal antibodies may represent Ehrlich’s “magic bullets” in therapy as well, but it is too soon to tell whether this exciting potential will be fulfilled.

During the 1970s, there was a flicker of enthusiasm for a discipline called “clinical immunology,” but it soon became evident that the breadth and depth of the field required immunologists trained in many different clinical specialties. The autoimmune (or autoreactive) diseases serve to illustrate the diverse manifestations of immunity gone awry. Ehrlich had been unwilling to accept such a concept, which he termed “horror autotoxicus.” Nevertheless, we now know that autoimmune disorders affect 5% of the population (two thirds of whom are women) and can damage virtually any organ or tissue in the body.

As noted, the immune system does not normally attack its own cells, i.e., “self.” Under some circumstances, however, self-discrimination fails. One mechanism for this failure involves “molecular mimicry,” by which viruses and bacteria display portions of their
structure that look like self; these areas cross-react with certain normal tissues and can damage them when an immune response to the nonself portion of the organism occurs. This molecular mimicry between microbial antigens and self may be important in the production of autoimmunity. Examples of autoimmune disorders are listed in Table 1. Specialists such as endocrinologists (insulin-dependent diabetes mellitus, Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, spontaneous infertility), hematologists (autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, pernicious anemia), rheumatologists (systemic lupus erythematosus, rheumatoid arthritis), neurologists (multiple sclerosis, myasthenia gravis), dermatologists (psoriasis, pemphigus vulgaris), nephrologists (poststreptococcal glomerulonephritis, Goodpasture’s disease), and others diagnose and treat patients with autoimmune diseases. In addition, it is clear that allergists, oncologists, infectious disease specialists, transplantation surgeons, and pathologists must be well grounded in immunology. Thus immunology has become recognized as one of the most important arenas of medical science. Emil von Behring, an immunologist, was awarded the first Nobel Prize in Physiology or Medicine in 1901. A total of 17 Nobel Prizes have been given to 1 or more individuals for their work in immunology and related disciplines (Table 2).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target</th>
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<tbody>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>Pancreatic beta cells</td>
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<tr>
<td>Graves’ disease</td>
<td>Thyroid gland</td>
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<td>Hashimoto’s thyroiditis</td>
<td>Thyroid gland</td>
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<tr>
<td>Addison’s disease</td>
<td>Adrenal glands</td>
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<td>Spontaneous infertility</td>
<td>Sperm</td>
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<td>Autoimmune hemolytic anemia</td>
<td>Red cell membrane proteins</td>
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<tr>
<td>Idiopathic thromboocytopenic purpura</td>
<td>Platelets</td>
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<tr>
<td>Pernicious anemia</td>
<td>Gastric parietal cells</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>DNA, other tissues</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>Connective tissue</td>
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<tr>
<td>Multiple sclerosis</td>
<td>Brain and spinal cord</td>
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<tr>
<td>Myasthenia gravis</td>
<td>Nerve/muscle synapses</td>
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<tr>
<td>Psoriasis</td>
<td>Skin</td>
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<tr>
<td>Pemphigus vulgaris</td>
<td>Skin</td>
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<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Kidney</td>
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<tr>
<td>Goodpasture’s disease</td>
<td>Kidney and lung</td>
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<tr>
<td>Rheumatic fever</td>
<td>Heart valves</td>
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With recent impressive advances in its sister sciences, molecular biology and genetics, immunology is now regarded by many as the centerpiece for future progress in medicine (13, 21, 22, 26-28). It now seems possible, even likely, that the immune system can be modulated, much like the switch that controls the intensity of light in a large auditorium. Three examples serve to illustrate this concept:

1. **Autoimmune diseases** in which self-recognition fails, and the body’s immune system attacks its own tissues and organs. Here the goal is to downregulate the immune response, thus reducing this destructive process.

2. **Organ transplants** in which, for example, a newly transplanted liver is recognized by the recipient’s immune system as “foreign” and therefore is rejected. Here the idea is to make the recipient “tolerant” of the transplanted foreign organ so it can function successfully in its new environment.

3. **Cancer** in which we need to boost the activity of the immune system so that the malignant cells can be effectively eliminated.

A crucial factor in all 3 of these circumstances, still unresolved, is to regulate the immune system in a specific manner so that only the unwanted response is altered—i.e., adjusting the intensity of a single bulb lower or higher while all the other lights in the auditorium remain on. Modulating the immune system in this way is a tall order indeed, but so was preventing smallpox and polio! One promising approach involves the use of dendritic cells, specialized antigen-presenting elements onto which various antigens can be loaded, which then direct a specific immune response or induce tolerance (29). Such an approach appears especially applicable to cancer and solid organ transplantation. We are fortunate to have Jacques Banchereau, a recognized world leader in this aspect of immunology, as director of the Baylor Institute for Immunology Research based in the new Lieberman Building.

Vaccines using dendritic cells and other elements of the immune apparatus are being developed and tested in a variety of disorders. The first trials with an HIV vaccine for AIDS have just begun (30). It remains to be seen whether these new efforts at immunologic
intervention will be successful (31). Perhaps Almroth Wright was right after all when he predicted that “the physician of the future will be an immunisator.”

Recent advances in immunology have brought scientific medicine to the dawn of a new age. The Baylor Institute for Immunology Research will bring together brilliant basic scientists and talented clinicians in a unique synergy. Their interaction will enable patients in the Dallas community and elsewhere to receive the most innovative and promising treatment available as we approach the twenty-first century. It is very likely that persons with cancer, organ transplants, autoimmune diseases, and other disorders such as infectious diseases and allergies will benefit from this exciting new Baylor program.

Acknowledgment

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References


