Chapter 1

Introduction — The Evolution of Our Understanding of the Immune System

The immune system has fascinated scientists ever since Sir Edward Jenner demonstrated the quantal (all-or-none) nature of protection against smallpox in 1798, over 200 years ago. Although it had been known for centuries that some diseases never strike twice, smallpox among them, Jenner demonstrated for the first time that one could achieve such protection artificially and safely by exposure to an avirulent form of the disease, a practice that came to be known as vaccination (from the Latin *vaccinus*, from cows).[1] Working meticulously in his medical practice in the English countryside, Jenner tested the well-known observation that milkmaids were immune to smallpox; provided they had previously contracted a self-limited pox disease from the udders of cows. Thus, Jenner showed that immunity to smallpox could be transferred to individuals who had never been exposed to either cowpox or smallpox by inoculating them with pus from milkmaids who had cowpox.

Exactly how the vaccine changed the host to confer this immunity from such a serious disease (smallpox accounted for 10% of the mortality in the 18th century), remained obscure for the next 150 years, only becoming known following work carried out over the last 30–40 years to identify and understand the immune system. For almost a century, smallpox was thought to be a special case, and nobody attempted to prevent additional epidemic or endemic diseases via vaccination. During most of the 19th century contagious diseases were thought to be caused by an imbalance of the four bodily humors (i.e. blood, yellow bile, black bile, phlegm) first proposed by Hippocrates

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(460–370 BC) two thousand years earlier. However, throughout the early and mid 19th century these ancient beliefs began to be questioned for the first time, and the germ theory of fermentation and putrefaction was formulated. Nevertheless, it was not until Louis Pasteur took up the debate in the late 1850s, repeating the earlier experiments of Schwann[2] and Cagniard-Latour,[3] that the "germ theory" became popularized and accepted as responsible for both fermentation and putrefaction, and also as a possible cause of contagious diseases.[4] Even so, the work of microbiology did not begin until another country doctor, Robert Koch, published his seminal experimental work in 1876, proving for the first time that a microbe actually causes the disease anthrax.[5,6]

Soon thereafter, Pasteur made the transition from chemistry to microbiology and then to immunology. In 1880, he revolutionized thought regarding immunity, by introducing the concept of attenuation of microbes using specialized cultivation methods, which in retrospect could never have attenuated the virulence of the bacteria he studied. Nevertheless, Pasteur extended Jenner's finding of vaccination to attenuated live bacterial vaccines, first for chicken cholera,[7] and then for anthrax of sheep and cattle.[8,9] Throughout Pasteur's studies, he maintained that only living organisms could confer protection via vaccination. Moreover, he was adamant that live organisms were required because "they depleted the host of vital trace nutrients" which were necessary for survival and multiplication of the organisms. Thus, the "father of immunology" was totally mistaken about how the immune system functions and how vaccination works.

In 1890, von Behring and Kitasato discovered antibody activity in the sera of immunized animals, thereby revealing that immunity occurs as an active process on the part of the host in response to exposure to foreign antigens.[10] Subsequently, during the first half of the 20th century, immunology focused on discerning the molecular nature of antibody activity, culminating in the 1950s with the demonstration by Tiselius and Kabat, as well as work by Porter and Edelman, that serum contains globular molecules, gamma globulins, which have the antibody activity, and that are comprised of two distinct chains (heavy and light chains).[11–13]

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Despite the promise of vaccination to rid the world of such serious contagions as tuberculosis and all acute bacterial infections, more than 50 years elapsed before another vaccine was realized. It proved more difficult to attenuate bacteria than Pasteur had prophesized, although a live attenuated vaccine against Yellow Fever, which was subsequently found to be due to a virus, was accomplished in the 1930s.[14] After the influenza pandemic of 1918, when approximately 40–50 million people perished worldwide, basic research focused on flu, and ultimately a filterable agent (now known as a virus) was identified as the causative microbe in the 1930s, thereby excluding a bacterial origin.[15,16] Then, during the Second World War, clinical trials conducted by Jonas Salk, among others, showed that influenza could be prevented by inoculation of a formalin-fixed, killed vaccine preparation grown in chicken embryos (disproving Pasteur's dogma that only living vaccines could work). These methods have persisted unchanged.

In 1957 MacFarlane Burnet proposed the Clonal Selection Theory of Immunity, which has served as the foundation for immunology to the present time.[17] Burnet first proposed that lymphocytes are the primary cells responsible for immunity. At the time, plasma cells had been known to be associated with antibody formation for almost a decade, attributable to seminal work by Astrid Fagraeus,[18] but plasma cells were not yet known to be derived from lymphocyte precursors. Fagraeus mistakenly assigned them to be derived from reticulum cells (macrophages) of the spleen. In addition, Burnet proposed that lymphocytes recognize foreign antigenic molecules by virtue of cell surface receptors, a concept suggested originally by Paul Erlich 50 years earlier.

Burnet also proposed that once selected by antigen, lymphocyte clones undergo a proliferative expansion, which allows the secretion of large quantities of antibody molecules that facilitate removal of the offending antigen. Moreover, he suggested that the expanded clones of antigen-reactive cells could then mount a more rapid and greater immune response upon reintroduction of the same antigen, thereby providing a cellular basis for the phenomenon of "immunological memory," the basis for vaccination. Accordingly, the proliferation of

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lymphocytes stimulated by antigen became one of the axioms of immunity.

To explain the phenomenon of the inability of the immune system to react with self-molecules, Burnet further predicted that self-reactive cells are deleted during lymphocyte development. Accordingly, Burnet ascribed "self–non-self recognition" to be a function of the cells and their surface antigen receptors. However, the molecular mechanisms whereby these cellular processes occur were left unexplained and remained unapproachable.

In 1960, Peter Nowell provided the first demonstration that lymphocytes are capable of proliferating in response to mitogenic lectins,[19] and others soon extended this observation to specific antigens,[20,21] thereby founding cellular immunology. Subsequently, in the 1960s Jacques Miller[22] and Max Cooper and co-workers[23,24] showed that there are two distinct immune systems, one responsible for the generation of germinal centers, plasma cells and immunoglobulin (Ig) molecules, and another under the control of the thymus, responsible for delayed-type hypersensitivity (DTH), cell-mediated immunity (CMI), allograft rejection, and graft versus host disease (GvHD).

Two distinct types of lymphocytes were subsequently found to be responsible for humoral versus cellular immunity. B cells, detected by their expression of surface Ig (as predicted by Burnet) differentiate into antibody-forming plasma cells.[25] By comparison, T cells, which mature in the thymus, were found to be identifiable by their surface expression of theta (θ) antigen and their lack of surface expression of Ig.[26] Moreover, these surface markers allowed the removal of each subset via lysis with antibodies and complement, thereby permitting the dissection of their respective roles in the generation of immune responses.

Hozumi and Tonegawa then made the startling discovery that the genes encoding the antigen-binding variable region of the Ig molecules are distinct from those encoding the constant regions and that during lymphocyte development the two regions rearrange to join one another.[27] This finding was unprecedented and explained how DNA rearrangement could contribute to the

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tremendous diversity of antibody molecules. These findings were then confirmed and extended using DNA cloning and sequencing methods.[28–30]

Also by the 1960s, once the nature of antibody molecules became known, immunologists turned their attention to the molecular nature of antigens. Early studies by Benacerraf and co-workers revealed that there was a fundamental difference between the antigens reactive with antibody molecules, which could be shown to be small chemical entities, termed haptens, versus large proteins, such as bovine serum albumin (BSA), termed carriers, which were required to elicit a typical CMI response detected by a delayed-type hypersensitivity (DTH) cutaneous reaction.[31,32]

It could be shown that even artificial polypeptides, and thus neither self nor non-self peptides, could sensitize a host to prompt a DTH reaction,[33] and furthermore, a minimum of only six amino acids was required.[34] Thus, it could be assumed that proteins could contain many distinct epitopes. Even more perplexing, Benacerraf and colleagues found that both humoral and CMI are genetically regulated by immune response (Ir) genes.[35] McDevitt then mapped the Ir genes to the major histocompatibility complex (MHC) locus,[36,37] while Benacerraf and co-workers demonstrated that histocompatibility between T cells and B cells was found to be required for the generation of antibodies.[38] Then, Rosenthal and Shevach found that histocompatibility between macrophages and T cells was required to elicit an antigen-specific T cell proliferative response.[39] These findings led to the hypothesis that perhaps there existed two receptors in the immune system, one that recognized peptide antigens, and another that recognized self-receptors encoded by MHC genes, and that all of the cells that cooperate in the immune reaction had to have the same MHC-encoded molecules. However, when Zinkernagel and Doherty found that viral T cell cytolysis of virus-infected fibroblasts also required histocompatibility between "killer" T cells and virus-infected target cells, it appeared that the T cell antigen receptor (TCR) might simultaneously recognize both peptide epitopes and molecules encoded by MHC genes via a single receptor.[40]

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Even so, the molecular nature of the MHC gene products that specified these genetic restrictions remained an enigma, as was the molecular nature of the T cell antigen receptor (TCR). Actually discovering the nature of these molecules became the Holy Grail of immunology. Using inbred (genetically identical) and congenic strains (genetically identical except for distinct chromosomal regions) of mice, Snell and others had mapped the chromosomal locus responsible for histocompatibility by performing skin grafts and tumor allotransplants in the 1940s.[41,42] Moreover, using antisera from immunized mice or from multiparous women, cell surface molecules were identified as histocompatibility leukocyte antigens (HLA) by Dausset, Strominger, Hood and others.[43–46] However, it was not until molecular genetics could be applied by Hood, Steinmetz and others in the early 1980s that the tremendous polymorphism of the MHC genes was appreciated (for review see Ref. 47).

The diversity of antigen recognition had led Burnet to predict that the "Clonal Selection Theory could never be tested experimentally unless in vitro culture methods could be developed that allowed for the creation of pure clones of lymphocytes."[48] Kohler and Milstein first satisfied such a condition for antibody-forming cells in 1975, by creating monoclonal antibody secreting somatic cell hybrids (hybridomas) between malignant proliferating plasma cells and antibody producing B cells from splenocytes.[49]

With regard to T cells, in 1965 two groups reported that medium conditioned by alloantigen-stimulated lymphocytes contained mitogenic factors.[50,51] Then, for the next decade numerous reports appeared of mitogenic activities in the conditioned media from leukocyte cultures, some thought to be derived from macrophages and others from lymphocytes.[52–58] Also, in the mid-1970s several groups showed that repetitive alloantigen stimulation could promote the growth of T cells in culture for several months.[59–61] Subsequently, Morgan and coworkers showed that lymphocyte-conditioned media could support the long-term culture of T cells from bone marrow, which suggested that the cultured cells might be derived from immature T cell precursors.[62]

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Because the prevailing immunological dogma indicated that only antigen was capable of promoting T cell proliferation, it seemed improbable that one could use the lymphocyte-conditioned medium to support long-term antigen-specific T cell proliferation. However, the very first experiments were successful,[63] as were cloning experiments that established the first monoclonal antigen-specific cytolytic T cells in 1979.[64] Accordingly, monoclonal hybridomas cells secreting antigen-specific monoclonal antibodies, and monoclonal T cells cytolytic for specific antigens, provided the data that proved Burnet's Clonal Selection Theory for both B cells and T cells. In addition, the capacity to grow and study antibody producing hybridoma clones, and antigen-specific functional T cell clones, ushered in the era of molecular immunology, which began in 1980 and is still ongoing.

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