from *AP Biology Professional Development Workshop Materials, Special Focus: The Immune System,* New York: The College Board (2005), pp.9-22.

Discovering the Self

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Sometimes the immune system doesn't seems like a system at all. Rather, it seems an odd patchwork of functions. Life-threatening allergic reactions occur alongside live-preserving immunity through vaccination. There is inflammation, identification of cancerous cells and removal of dead cell material. The apparent lack of coherence in this hodgepodge of roles certainly adds to the challenge of teaching about the immune system. To express unity in the suite of functions, many biologists adopted the dual notion of 'self' and 'non-self'. In this view, the immune system fundamentally discriminates between the body's own proper functioning cells ('self') and foreign pathogens, toxins, renegade cells and waste fragments (all 'non-self'). It then triggers an appropriate response — sometimes narrowly targeted, sometimes broad; sometimes local, sometimes systemic. By exploring the history of the concept one might clarify (towards more fruitful teaching) just what an 'immune self' means.

One may wonder, too, given the apparent chaos and diversity of immune responses, how scientists ever developed an effective concept. Tracing the origins of our understanding takes one back and forth through history. One encounters several Nobel-prize winning discoveries, as well as many apparently insignificant details. The excursion can provide deeper perspective on scientific practice, often hidden by the polished textbook concepts.

Tolerance and the Non-Nonself

The concept of self ultimately emerged from an unlikely source. Ray Owen grew up on a farm. In graduate school, he turned to the genetics of blood type in cattle. In 1945, he studied a case of fraternal twins. In Mendelian terms, individuals with distinct fathers should exhibit unique blood types. Yet here, Owen found, each twin could accept blood transfusions from the other. They *shared* blood type! Owen noted that they could carry each other's antigens because in cattle such twins share placental circulation. Their blood type thus resulted from development, not solely genetics.

Owen's observation gained further significance through Frank Macfarlane Burnet, a physician thinking about how antibodies are produced. Burnet saw here a general feature of immune systems. Each twin had acquired what he called *tolerance* to the other's antigens. At a critical early stage, organisms might not yet recognize the potential antigens as 'non-self'. Later, they would accommodate the already introduced antigens as 'self'. The idea echoed the concept

of behavioral imprinting, then being developed coincidentally by Konrad Lorenz. Burnet tried—unsuccessfully—to immunize chick embryos against influenza in 1947. A sense for nonself was not yet evident. 'Self', Burnet concluded, was *learned*.

Burnet came to view immune identity as determined at birth. The prevalent idea about antibody production, however (advocated by Linus Pauling—and Burnet too), was *instructional*. That is, specific antibodies would form just when antigens were introduced. A new protein would use the antigen as a template, folding specifically to match it. (The discoveries about DNA, RNA and protein synthesis were still several years away.) Burnet soon adapted Neils Jerne's 1955 model based on natural selection. He envisioned an initial repertoire of antibodies, where individual variants—constitutively present—would be "selected" when encountering new antigens. The antigen-specific cells would proliferate; some clones would remain as enhanced "memory": the clonal selection theory, now described in textbooks. But Burnet was still oriented to 'self' as central:

> The first requirement of an adequate theory of antibody production is to account for this differentiation of function by which the natural entry of foreign microorganisms or the artificial injection of foreign red cells provokes an immunological reaction while the physically similar autologous material is inert.

To explain tolerance, then, Burnet assumed that clones of self-reactive cells were deleted from the repertoire prenatally. However, he did not detail how. The problematic nature of that omission would unravel only much later. For Burnet, then, clonal deletion implied the body's immune 'self' was negative: tolerance reflected an *absence* of 'non-self' response. For his interpretation of immunity as knowledge of 'non-self' and of tolerance as 'self', Burnet shared the 1960 Nobel Prize in Medicine.

The Nobel award also acknowledged complementary work by Peter Medawar. Treating wounds in World War II, especially burns from the new incendiary bombs, had highlighted the importance of transplants and skin grafts. In the early 1940s, therefore, Medawar had reoriented his research towards understanding why transplants frequently failed. What critical physiological factor had they missed? In studies on different strains of mice, skin grafts were accepted from elsewhere on the same body or from the same strain, but not from different strains. Transplants, he concluded, were *actively* treated as foreign. Tissue rejection was, surprisingly, an *immune* response. Medawar went on to profile a cell-mediated response, different from humoral responses. More than a decade later others would articulate the distinction between B- and T-lymphocytes. The fundamental unity behind the two responses, however, would not be evident for quite some time.

After Burnet presented his ideas of 'self' in 1949, Medawar and his colleagues returned to his skin graft studies to demonstrate immunological tolerance experimentally. Using Owen's study of cattle twins as a model, Medawar cross-injected mice embryos with cells from other strains. He confirmed that early introduction of antigens enabled allografts across strains—transplants that were rejected in unprimed controls. Immunological functions of self and non-self thus occurred both in humoral and cell-mediated contexts.

Identifying Nonself

Burnet's notion of immune self underscored the challenge of differentiating specific cells. A solution had already been developed in another context, decades earlier, by Paul Ehrlich.

Ehrlich entered science through chemistry. He first worked on aniline dyes. Using such dyes as histological stains in the 1880s, in fact, he identified and named the various white blood cells (basophils, neutrophils, etc.). Applying the stereochemical idea of specific shape in space, Ehrlich conceived dyes as 'amboceptors': one end of the molecule attached to the cell, the opposite end held a distinctive color. Later he thus had a ready explanation for how antibodies could recognize specific diseases. His 1900 diagram of cells with different molecular side-chains extending from its surface (see Figure 1) became a popular icon—and one easily interpreted even now, over a century later. Antibodies with specific shape extending from a cell surface would lock onto some toxin or foreign element. After production and release, the other end of the antibody allowed for immunological action — for example, the complement reaction, recently discovered in 1899. Ehrlich showed how one nonself was differentiated from another nonself. In Burnet's context, the shapes would also distinguish self and non-self. Here, the mechanism of identifying self would later prove to be more complex and indirect, even to the extent of (again) viewing these early models as misleading.

Molecular shape was key in Ehrlich's and subsequent conceptions. The term 'self' can easily evoke anthropomorphism. One may mistakenly imagine immune cells as having visual or other conscious awareness. Ehrlich's model of complementary shapes showed how cells functioned "blindly" through unintentional collisions. In relying on molecular shape, immune cells also cannot recognize a whole entity as 'non-self'. Rather, they respond to fragments or molecular "handholds"—what Neils Jerne labeled an 'epitope' in the 1970s. Jerne also underscored the image of nonself as a constellation of antibody "cavities" distributed across cells throughout the body—what Jacques Oudin earlier had called the collective 'idiotype' (here and elsewhere I use the term 'antibody' to denote loosely any immunoglobulin). Some fragmentary images are unique. Others are not. They may be shared by related organisms or mimicked via

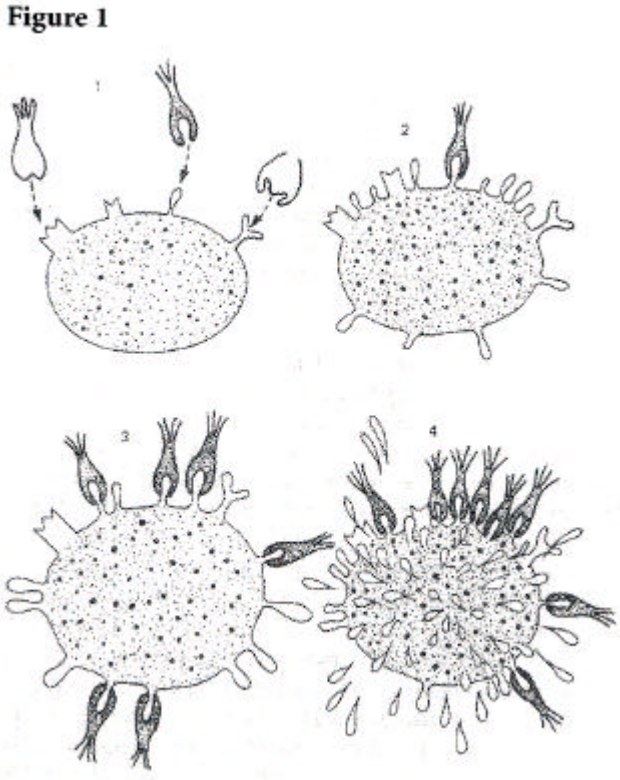


Figure 1. Paul Ehrlich's 1900 diagram of the specific side-chains of antibodies on the cell surface, leading to their selective proliferation and release. Contemporary Jules Bordet complained: "By the abuse that it has made of quite peurile graphical representations which merely translate the exterior aspect of phenomena without in any way penetrating to their inner meaning, it has extended the desceptive use of explanations that are facile, but illusory."

natural selection. Identification is inevitably partial and indirect, hence not always reliable.

For Ehrlich, antibody fit was also exact and unerring—and strictly chemical (through bonding). Yet others at the time borrowed from colloid chemistry (with no sophisticated sense yet of macromolecules or protein configuration) and saw the interaction as physical and variable. Two shapes could thereby exhibit *relative* degrees of fit. An antibody for one antigen, for example, might "cross-react" with similar but not exactly matched antigens. The image of nonself contingent on shape was sometimes "fuzzy" and hence fallible. Today, the role of molecular shape seems ubiquitous: enzymatic catalysis, DNA transcription and replication, multimeric protein assembly, neurotransmitter signals, hormone receptors, genetic inducers, enzyme repressors, etc., all function through complementary fit. Loose and tight fits, well exemplified in immune recognition of nonself, allow for some functional fuzziness—and occasional mis-cues.

Responding to Nonself

Focusing just on the nature of nonself signals may easily eclipse complete understanding of the function of the immune self. One may overlook the context: the corresponding response. The body also disables or eliminates nonself. Indeed, this conceptual eclipse occurred early last century, after several noteworthy discoveries by Ilya (later Elie) Metchnikov. Metchnikov's original interest was invertebrate zoology. He studied especially digestive processes, which included wandering phagocytes in the mesoderm. Metchnikov recalled how his research became reoriented while at a Mediterranean field station in the late 1870s:

> One day when the whole family had gone to the circus to see some extraordinary performing apes, I remained alone with my microscope, observing the life in the mobile cells of a transparent starfish larva, when a new thought suddenly flashed across my brain. It struck me that similar cells might serve in the defense of the organism against intruders. Feeling that there was in this something of surprising interest, I felt so excited that I began striding up and down the room and even went to the seashore in order to collect my thoughts.

He immediately tested the idea by introducing a splinter into the starfish's body. He later observed the specialized cells surround it. With further research, Metchnikov proposed that inflammation was not a feature of disease, as commonly believed. Rather, the local flourishing of phagocytes was an active response by the organism. As a Darwinian, he went on to speculate on the origin and evolution of the immune system, based on the digestive functions he had observed in invertebrates. He continued study on anthrax bacteria, which resist lysis and succumb only to phagocytosis. Although anthrax (we now know) is unrepresentative, ironically it supported Metchnikov's emphasis on phagocytosis as central, even for specific diseases. Metchnikov's interpretation of inflammation eventually triumphed, earning him a Nobel Prize in 1908.

Ironically, Metchnikov shared the Nobel award with Paul Ehrlich, who harshly denigrated his ideas. Ehrlich epitomized a contrasting, growing tradition from germ theory based on chemical approaches to immune responses and specific diseases. Antibodies were discovered in 1890. In the years following, Emil von Behring and Shibasaburo Kitasato demonstrated that one could thereby transfer immunity to diphtheria or tetanus passively from organism to organism. Cell-free blood sera could substitute for vaccination. Von Behring would be honored with the very first Nobel Prize in Medicine in 1901 for his development of serum therapy, then hailed as a

means for conquering all infectious disease. In the same decade, Ehrlich showed how to quantify diphtheria toxin and its antibodies through titration. Agglutination, bacteriolysis (via complement) and hemolysis—all cell-free processes—were elucidated. Diagnostic tests using anti-sera were on the horizon. Humoral concepts were leading to fruitful research and therapies. Metchnikov's focus on cells seemed redundant. Enthusiasm for his cell-oriented perspectives waned and related research opportunities remained overshadowed for several decades.

Some scientists at the time did try to reconcile humoral and cellular approaches to immune function. Notable among them was Almroth Wright, profiled by his friend George Bernard Shaw in the 1906 drama, *The Doctor's Dilemma*. As described by Shaw in his "Preface on Doctors," Wright "discovered that 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 opsonin." Opsonin as a unique humoral chemical was elusive, although coating cells with antibodies does facilitate phagocytosis, just as Wright claimed. Wright's theory was not well received—perhaps due to the humoral fervor of the period, perhaps due to his increasingly baroque conceptualization, or perhaps for both reasons. Although knighted, Wright became known as "Sir Almost Right." (Scientists, it seems, are not above name-calling.) Regardless, opsonization as a process is still described in today's textbooks. Wright's core idea, still valid, helped link an antigen to its removal. Such response is essential to characterizing the functional nonself fully.

Beyond Antibodies and Lymphocytes

Burnet's concept of self established a basic framework. Yet his interpretation may also seem simplistic, given today's knowledge. Of course, many discoveries since have deepened our understanding. Some have even transformed what once seemed foundational. For example, the self/nonself distinction might seem to imply that an immune system never targets the body's own cells. Indeed, an appreciation of autoimmune diseases emerged only haltingly, after many puzzling examples began surfacing in the mid-1940s (mostly diseases regarded as peripheral, such as hemolytic anemia, encephalomyelitis, sympathetic ophthalmia and phacoanaphylaxis). To some degree, these diseases made more sense using tolerance as context. That is, the pathology, or violations of an expected tolerance, helped underscore the healthy condition. In other cases, however, eliminating some of the body's own cells seemed adaptive. Burnet's scheme of clonal deletion itself implied such selective cell removal. Researchers soon found cell-mediated immune responses that targeted tumors and viral infected cells, even though such cells are not strictly foreign. Even uninfected cells, once dead, are cleared by macrophages. Thus, immune responses did not align simply with genomic identity or the individual organism. Instead, the *immune* self seemed more about physiological integrity.

Burnet's focus on antibody production may also seem to imply that antibodies alone *define* an individual. One might imagine that antibodies, as their name apparently suggests, are produced only to nonself "bodies" and, further, that nonself cannot be recognized without them. Such inferences would prove mistaken historically. Antibodies against the self were identified—not unexpectedly—in various autoimmune conditions. But researchers also encountered another remarkable set of antibodies. Here the "internal" antigens (self) were antibodies themselves. What resulted was an *anti*-antibody! (The term, despite its potential to confound, seemed inevitable.) Evidence for anti-antibodies emerged unexpectedly while focusing on several unrelated problems. In 1963-64 two labs examining immunization with antibody-coated bacteria

found immunity specific not to the bacterium, but to the active site of the attached antibodies: another anti-antibody. Meanwhile, a third lab initially investigating myeloma proteins generated antibodies to stereoisomers. Each antibody, in turn, generated its own distinct anti-antibody: a definitive stereochemical pair. In 1957, work on red blood cell agglutinins had indicated that rheumatoid factor may have been formed by an immune response to denatured gamma globulin. An anti-globulin antibody would lead to an immune deficiency (strangely through autoimmunity!). Anti-antibodies were certainly beyond what Burnet anticipated.

As a class, anti-antibodies are special indeed: they can exhibit and thereby preserve the shape (or epitope) of the original antigen. Antibody and anti-antibody can thus, paradoxically perhaps, interact immunologically. In the mid 1970s Neils Jerne, echoing earlier speculations (by at least Victor Najjar in 1955 and Alexandre Besredka in 1901), explained how such mutual interaction could regulate immune responses. Complementary immune cells would cross-check each other until excess antigen tipped the balance. Jerne's theory offered a prospective alternative mechanism for tolerance. Antibodies against self (*auto*antibodies) need not be completely eliminated. Rather, their activity could be suppressed by a set of anti-antibodies. Tolerance would reflect a form of immunological equilibrium; autoimmune conditions, a disruption of that balance. Accordingly, tolerance might well be acquired in adults, a therapeutic promise for transplantation that still beckons. In contrast to Burnet's notion, autoantibodies may be quite common, perhaps even the norm. The immune self (expressed as tolerance) may emerge from regulatory balance, not the mere presence or absence of specific antibodies. For these and other insights, Jerne received a Nobel Prize in 1984.

The roles of antibodies became further narrowed when biologists observed responses to nonself without them—and even without the lymphocytes that produce them. By the mid 1970s immunologists had distinguished between B-cells and T-cells and catalogued the functions of the various T-lymphocytes. Cells seem to be destroyed only by antigen-mediated T-cells. Several laboratories, however, documented exceptions. The discovery of 'natural killer cells' (NK) and their properties were persuasively consolidated in 1975. The cells had lurked in images of the blood for years, virtually unnoticed. Later researchers identified the NK's nonself "cue" as interferon released from the infected cell itself. Immune response here involved identifying a general type of nonself, rather than particular pathogens.

Even more striking was a report by Edwin Cooper in 1974 of graft rejection in earthworms. Later grafts from the same source were rejected more swiftly. In vertebrates, such responses to nonself involve lymphocytes. Yet annelids have simpler immune systems—without such cells and without immunoglobulins. Even organisms with no antibodies could respond effectively to nonself. Metchnikov's largely buried work with invertebrates suddenly seemed relevant again. For example, sponges can reaggregate from individual cells, even when cells of different species are mixed. Sponges, too, recognize self and nonself. The species sort themselves through chemical recognition and chemotaxis, hallmarks of some immune cells even in vertebrates. Gerald Edelman (who shared a Nobel Prize for describing the chemical structure of antibodies) suggested in 1987 that immunoglobulins might derive from cell adhesion molecules, indicating a possible origin and further functional allegiance of the immune self. If such evolutionary perspectives are warranted, then the system of lymphocytes—so critical in our conception of immune memory, for example—may not be central or even essential to self/nonself determination. Rather, antibodies would be a highly derived mechanism, primarily to enhance preexisting responses. Studies in immune phylogeny thus hold great promise for

clarifying the fundamental versus derived functions for self and nonself. Echoing Metchnikov's aims, comparative immunology may help unify the current ad hoc division between a 'specific' self (enlisting lymphocytes and cytokines) and a 'non-specific' self (using macrophages, histamines, etc.).

Self *AND* Nonself

The most recent developments in conceptualizing the immune self involve the histocompatibility complexes (MHCs) (see also the accompanying essay by Eileen Gregory). Here, early clues emerged from studies on the genetics of cancer. By the 1930s medical researchers knew that susceptibility to tumors was partly heritable. To facilitate genetic study, George Snell had just developed a few congenic strains of mice (similar in all but one gene). Peter Gorer adopted them for his studies. As a peripheral project for personal interest, he also explored the mice blood types, not yet known. He identified three antigens. When Gorer completed his genetic analysis in 1937, he found that resistance to tumors (introduced as transplants) correlated with blood type, specifically the second antigen! Meanwhile, Snell's own research had isolated a locus affecting tumor transplantation that he labeled (appropriately enough) 'H', for histocompatibility. Gorer and Snell had identified the same gene, ultimately named H-2. Only later would they discover that Gorer's antigen was not exclusive to blood cells, but present on virtually all cells (tumor cells, as well). Because they were focusing on tumors and genes, the significant immune link between antigen and transplantation largely escaped their notice. But they had happened into what would eventually be interpreted as a key molecular marker of self: MHC I.

Histocompatibility challenged the growth of transplant surgery. Matching tissues—in a sense, looking for a similar 'self'—became a major task. But the natural function of the MHC surfaced in quite a different context. In the early 1960s Baruj Benacerraf was studying antigen recognition in delayed-type hypersensitivity (allergic-like reactions, epitomized by poison ivy dermatitis, that develop only after 1 to 2 days). Such responses had already been traced to cell-bound receptors. Benacerraf wanted to decipher the structure of the presumed antibody. He tried to establish some uniformity by attaching antigen fragments to a homogenous protein base (he chose poly-L-lysine). But when he injected the synthetic antigens under the skin of his guinea pigs, the response was far from uniform. Indeed, Benacerraf noted, some strains mysteriously had no immune response at all. Moreover, different protein "carriers" elicited response (or no response) based on the strain. The immune response *also* depended on the protein carrier. The carrier, being strain-specific, was genetic. Although Benacerraf's results remained confusing for some time, they largely established that recognizing an antigen involved two distinct components. One was the nonself antigen and the other was a genetically compatible protein.

The puzzle was further resolved through studies in the mid 1970s on lymphocytic choriomeningitis virus (LCMV), which causes chronic inflammation in the brain. Peter Doherty was already working on the virus in mice when Rolf Zinkernagel arrived as a graduate student, fortuitously bringing relevant skills in assaying. They decided to collaborate. Soon, they induced formation of LCMV-specific killer T-cells. They measured their efficacy *in vitro*. Then, following a cue that susceptibility to LCMV (like Gorer's and Snell's cancer) seemed related to MHC make-up, they turned to assaying the relative effectiveness of their T-cells' on other strains of mice. But the T-cells were completely ineffective. Reciprocal experiments (using T-cells induced in the other strain) likewise did not lyse cells of the first strain. T-cell function was

discretely MHC-restricted. After eliminating a few other possibilities, Zinkernagel and Doherty concluded that the MHC was as essential as the antigen in identifying target cells. MHC did not exist simply to confound transplant surgeons. Rather (further studies confirmed), it was a self marker integral to identifying nonself. The deeper significance of the discovery, however, would emerge only as researchers continued to encounter this dual identification elsewhere. For example, Benacerraf's carrier protein was indeed MHC. There was a parallel system in B-cells, using another set of histocompatibility proteins. Dual recognition also seemed to guide various stages of both stimulus and response. Ultimately, self and nonself seem intimately coupled through the role of MHC. The Nobel Foundation honored the achievements of Benacerraf and Snell in 1980 (Gorer had died) and Doherty and Zinkernagel in 1996.

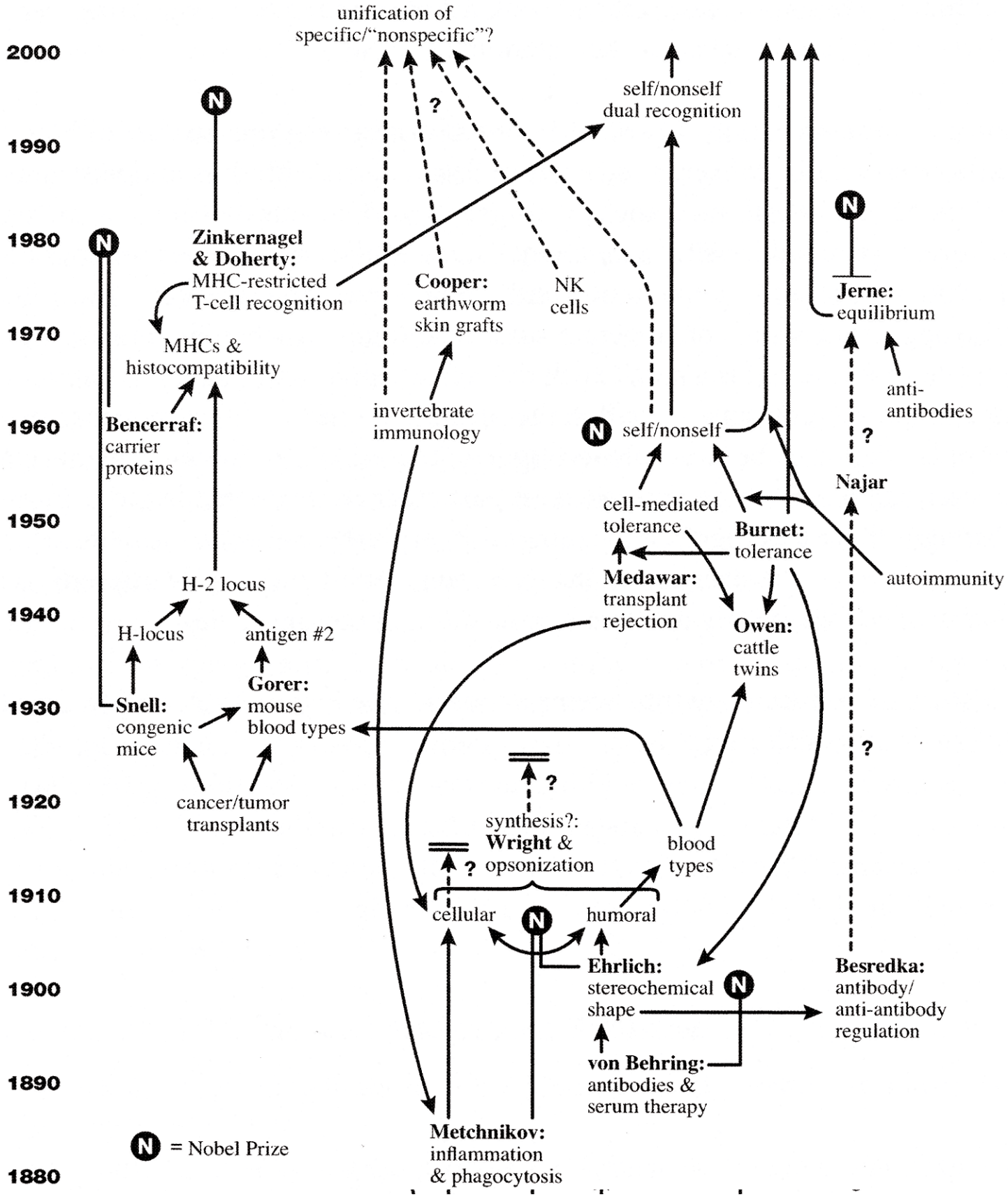
The Nature of Self and the Nature of Science

The history highlights the concept of self as central in interpreting immune function. Like so many other biological processes, complementary molecular shapes are fundamental. Identifying self and nonself is particular, yet fragmentary. It can be both "fuzzy" and mistaken. A genetic framework for self (MHC) functions in tandem with a learned component to specific nonself (via antibodies). The self is dynamic. Responses are regulated. Together, they help maintain an integrity of properly functioning cells, although the system has many ways to fail.

Where did our conceptions of self and nonself originate? —From studies of blood type in cattle twins and in congenic mice. —From fascinations with dyes and with starfish digestion. —From clinical medicine and surgery and the natural history of sponges and earthworms. —From addressing prominent diseases, like cancer, and the more obscure, such as meningitis and sympathetic ophthalmia. —From the exigencies of war wounds and the opportunities of convergent resources and talents when people meet. The concept of immune self is a pastiche derived from many sources. The student of science might thereby appreciate that the process of science differs remarkably from the popular rhetoric about simply testing hypotheses. While strategically designed tests were essential, science here also relied on particular contexts that led to experiments and brought them together in a meaningful interpretive network. Insights arose from shifts of context and convergences that were unplanned and largely unpredictable. The discovery of self was partly due to a constellation of contingencies.

The history of immunology thus seems a mosaic. A simple timeline would be deeply misleading. The concept of self did not unfold one step to the next in a steadily progressive series. Rather, research proliferated on numerous paths. Some results inspired further studies. Others lay dormant. Decades later, an intersecting investigation recovered the latent findings, linking disparate research lineages. Such connections were not always clear in advance. No method easily discerns dead ends from loose ends. Nor could one know which studies deserved the foreground. Comprehensive histories of immunology written in the late 1980s, for example, barely mentioned the 1973-75 work of Zinkernagel and Doherty: even Nobel-caliber achievements may take decades to appreciate. The persistent discord between Metchnikov's and Ehrlich's traditions illustrates how findings must also be integrated, even if the raw knowledge exists. Synthesis was essential in retrospect, but hard to foresee. Scientific research weaves unexpectedly across diverse fields and phenomena. The history of science may thus be as complex as the immune network itself.

A final pair of lessons about the nature of self and the nature of science lies in the very name of the immune system. Quite early in history, humans noticed that those who did not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unification of specific/"nonspecific"?
self/nonself dual recognition
Zinkernagel & Doherty: MHC-restricted T-cell recognition
Cooper: earthworm skin grafts
NK cells
Jerne: equilibrium
anti-antibodies
MHCs & histocompatibility
Bencerraf: carrier proteins
invertebrate immunology
self/nonself
Najar
cell-mediated tolerance
Burnet: tolerance
autoimmunity
Medawar: transplant rejection
Owen: cattle twins
H-2 locus
H-locus
antigen #2
Gorer: mouse blood types
Snell: congenic mice
cancer/tumor transplants
synthesis?: Wright & opsonization
blood types
cellular
humoral
Ehrlich: stereochemical shape
Besredka: antibody/ anti-antibody regulation
von Behring: antibodies & serum therapy
Metchnikov: inflammation & phagocytosis
= Nobel Prize

succumb to a disease dramatically escaped subsequent epidemics. Eventually, borrowing from the medieval legal concept of 'exemption', they called such capacities *immunity*. And so the immune system was labeled: based (in modern terms) on physiological memory of a specific nonself. Yet now immune memory constitutes only a narrowly specialized branch of a larger system. Ironically, immunity seems a poor model for understanding the "immune" self. Further, although the study of infectious diseases, vaccinations and germ theory led scientists into immune processes—with the renowned discoveries of Jenner, Pasteur and Koch—it was the cell-mediated contexts (transplants, delayed hypersensitivity, etc.) that proved critical in plumbing the core of the immune self (through discoveries of tolerance and MHC). Equally ironically, research need not identify the most basic first, then fill in the details. What is obvious or easiest to learn may not be the most important or fundamental. Thus, when knowledge grows, sometimes concepts shift emphasis. As patterns fill in, the image may switch. A thrilling new gestalt may emerge. Burnet's early notions of self hardly seem warranted now, despite their benchmark role. Tolerance and definition of self may occur throughout life. Autoantibodies can be functional. Histocompatibility proteins are as essential as antibodies. Yet the reconceptualizations nonetheless extend and echo Burnet's original principle of self and nonself. Science evolves. Experiments reveal new details. Early ideas give way. Perspectives transform. The potential for error and with it unanticipated discovery is what makes science so exhilarating.

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