

## AUTOIMMUNITY SHIFTS PARADIGMS

IRUN R. COHEN

Department of Cell Biology, The Weizmann Institute of Science, Rehovot, Israel

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A scientific paradigm is a conceptual model for sorting experimental observations into meaningful categories. To be successful, a paradigm has to fulfill two conditions: it has to be logically plausible and it has to account for the observable. A paradigm is modified or replaced when it fails to account for the facts. Let us consider paradigms designed to explain autoimmune disease.

### The Causal Connection

No immunologist would object to the statement that autoimmune disease follows from autoimmunity, as depicted by the arrow in Proposition [1]:

[1] Autoimmunity  $\rightarrow$  Autoimmune Disease.

The proposition seems simple but it makes a great difference how one interprets the meaning of the arrow: What is the causal relationship between *autoimmunity and autoimmune disease*?

Macfarlane Burnet (1), and immunology in his wake, saw the connection between the terms of proposition [1] as both necessary and sufficient: Autoimmune disease was inconceivable without a preceding state of autoimmunity (*necessary*); and a state of autoimmunity was inconceivable without an attendant disease (*sufficient*). In other words, if *autoimmunity* then autoimmune disease. As autoimmune disease does not occur in most individuals, it was assumed that autoimmunity was absent from the healthy immune system.

No immunologist would object to the statement that a state of autoimmunity follows from the existence of lymphocyte clones that recognize self, as depicted by the arrow in Proposition [2]:

[2] Self-recognition  $\rightarrow$  Autoimmunity.

The Burnetian paradigm would also interpret the arrow of proposition [2] as a causal connection: the presence of autoimmune lymphocytes suffices and necessarily produces a state of autoimmunity. In other words, if *self-recognition*, then *autoimmunity*. Thus, if the healthy immune system does not admit autoimmunity, the healthy immune system must not admit self-recognizing lymphocytes, "forbidden clones" in the parlance of the Burnetians (2).

Proposition [3] would be acceptable to all rational people and not only to immunologists.

[3] Self and not-self are distinct entities.

Since *self* and *not-self* are mutually exclusive classes, proposition [3] is tautologically true: self (S) does not include *not-self* (NS), or  $S \neq NS$ .

Self here refers to the immunological self and not-self to the immunologically foreign. Indeed the classes of self and foreign (not self) are defined immunologically by the antigens in each class. In other words, proposition [3] may be interpreted immunologically to mean that self antigens are essentially distinct from not-self antigens. Orthodox Burnetians would extend the idea of proposition [3] to conclude that the immune system, which defines antigens, exists to discriminate between self and not-self. Immunology has been called the Science of Self-Nonself Discrimination (3).

Address for correspondence: Dr. I.R. Cohen, Department of Cell Biology, The Weizmann Institute of Science, 76100 Rehovot, Israel.

### Logical But Wrong

Propositions [1], [2] and [3] and the conclusions they entail create a logically compelling paradigm that has characterized immunological thinking for three decades. This paradigm has dispossessed autoimmunity into the realm of accident, an unforeseeable event blamed on random errors in the otherwise ordered process of self tolerance (1,2). For this reason it has been difficult for immunologists to face up to the fact that the immune system publicly ignores or contradicts all three propositions. Contrary to propositions [1] and [2], *Autoimmune Disease* does not follow automatically from the existence of *Autoimmunity*. In fact, self-recognizing lymphocytes and natural autoimmunity are universal characteristics of healthy immune systems (4). However, only when the phenomenon of natural autoimmunity is admitted into the realm of canonical immunology, can natural autoimmunity then become a fitting subject for scientific investigation: what is the nature of naturally autoimmune lymphocytes, what is their origin, and what purpose do they serve? Which antigens do they recognize and why? How are autoimmune lymphocytes regulated and controlled? Are they the source of autoimmune diseases? If so, how, why and when?

I suspect that propositions [1] and [2] are contradicted in practice by the immune system because proposition [3], although true in the formal sense, is wrongly applied to the immunological world. Quite simply, *self* and *not-self* cannot be distinguished absolutely by virtue of their antigens. The genetic conservation of the biosphere guarantees that foreign organisms will contain self or self-like antigens. Epitopes are shared between parasites and hosts. Now if self antigens are included in the foreign (not-self) environment, then regulated autoimmunity must be built into the immune system. Regulated autoimmunity allows the system to fight infection by self-mimicking parasites while preventing the emergence of unregulated autoimmune disease.

The Burnetian simplification was the idea that self could be distinguished from *not-self* by the antigen receptors or antibodies alone. This simplification led to the fallacy that only the antigen receptors and antibodies could distinguish between *self* and *not-self*. This is a fallacy because the class of molecules in the *self* and the class of molecules in the *not-self* include

some member antigens and many member epitopes in common. Thus self is certainly not not-self, but the absolute distinction cannot be made by lymphocyte receptors and antibodies alone. Proposition [3] is a truism, but it is not applicable to the antigen-receptor world of immunology. Elsewhere I have developed the idea of the Immunological Homunculus (5,6) to consider how natural autoimmunity (the contradictions of propositions [1] and [2]) may be required to deal with the inapplicability of proposition [3] to the antigens. Indeed, the distinction between *self* and *not-self* is a matter of *context*, not only of antigens, but that is beyond the scope of the present discussion.

### Shifting the Paradigm

The problem with an esthetically logical paradigm is that it can blind the observer to the observable: you don't see what is not supposed to be there. Some may tolerate blind spots in matters of religion or esthetics; as the little boy said, "faith is believing what you know ain't true". But preconceived notions in science are dangerous; they can sabotage the scientific method. Fortunately, science predicts the obsolescence of its paradigms. Science looks to the revision or replacement of its most cherished ideas. Science has no difficulty casting off worn out ideas; the difficulty is the scientist's. To paraphrase the little boy quoted above: to advance science, the scientist must see what he knows ain't there.

The author is the incumbent of the Mauerberger Chair of Immunology and the Director of the Robert Koch-Minerva Center for Research in Autoimmune Diseases.

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