The Limits of the Self: Immunology and Biological Identity

Thomas Pradeu
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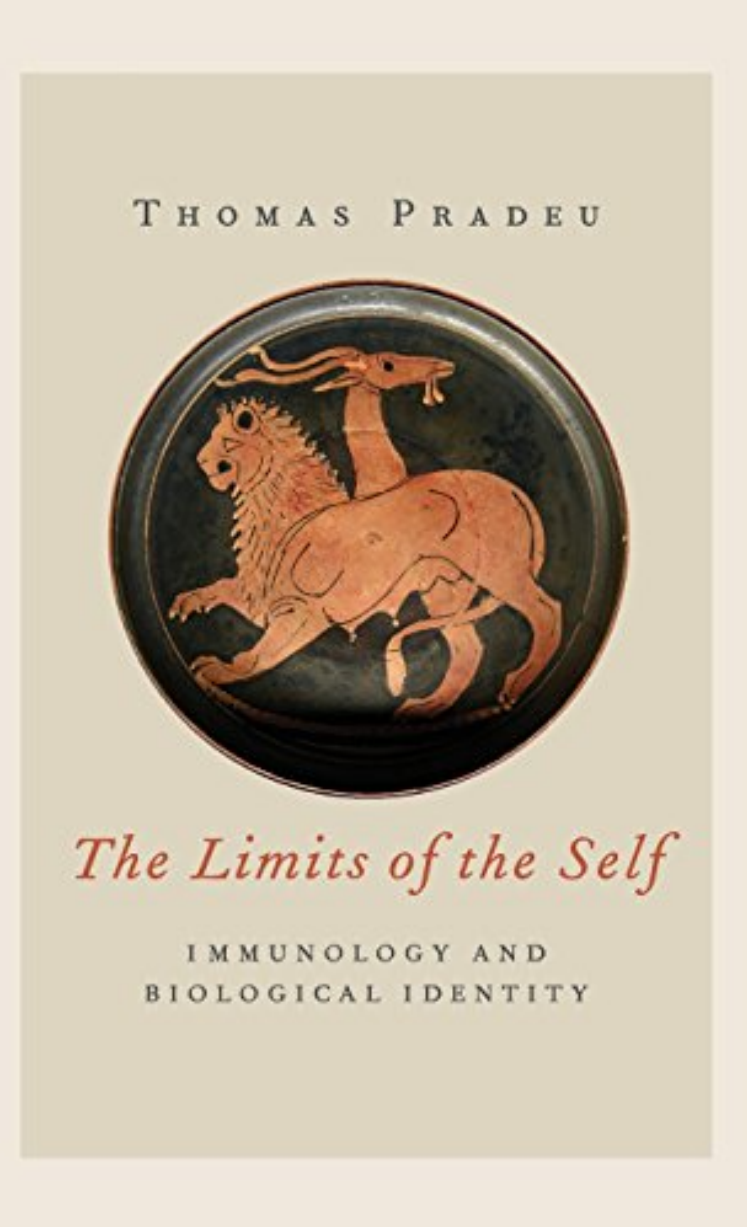

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Thomas Pradeu : The Limits of the Self: Immunology and Biological Identity before purchasing it in order to gage whether or not it would be worth my time, and all praised The Limits of the Self: Immunology and Biological Identity:

2 of 2 people found the following review helpful. Creative argument for letting your "self" goBy A. J. SutterThis book makes a clear and persuasive case for changing how we think about physiological immunity. The argument isn't limited to topics of clinical significance, but could also affect how we conceptualize biological evolution. While it's not exactly a book of popular science for a general readership, a specialist background in medicine, biology or philosophy isn't necessary for enjoying it. Possibly an undergrad course in human physiology might be enough; in my case I got by with some dimly recalled facts about immunology picked up from skimming the easy pages at the front of Science and Nature, and a couple of books worth of reading in philosophy of biology (evolution and genetics) in the not so recent past. As it turns out, I was fascinated -- even hitting the pause button on a pretty good novel for a couple of days because I was so eager to follow this book through to the end.The book's contents fall almost exactly into two halves: first a critique of the prevailing notion of immunity, known as "self-nonself," and then a constructive argument for an alternative that the author (TP) calls, at least provisionally, the "continuity theory." The book opens with a review of the history of theories of immunity, and a rough outline of the facts of the immune systems in humans, plants and insects. TP next lays out the main tenets of the self-nonself theory. In essence the theory says that the immune system has a way of recognizing "self," which is determined mainly during development before birth, and that it will mount a systemic immune reaction against "non-self" that it encounters thereafter.TP focuses especially, and with great respect, on the original formulation of the theory by Sir Macfarlane Burnet (1899-1985, Nobel 1960), who worked on it from the late 1930s until the end of his professional life in the 1970s. In his early articulations of the theory, Burnet seemed to formulate a notion of "self" that even extended to unicellular animals: e.g. an amoeba is able to digest things it ingests by phagocytosis, but doesn't digest itself. Later in his career Burnet tended to construe self in the more limited context of acquired immunity and the "clonal selection" of antibody-producing cells (the notion that the body randomly produces a broad spectrum of antibodies before it actually encounters the various antigens that fit into them, and later selectively amplifies the ones it needs). This kind of immunity, and therefore this notion of "self," exists only in vertebrates with jaws. One of the problems the theory must solve, as must any theory of immunity, is to explain how the body tolerates the "self" and certain other things it encounters, such as an embryo or fetus (which is only half "self" of the mother), certain tumor cells, and so on.TP takes the view that Burnet formulated many brilliant questions, especially in the early version of the theory, but that his answers aren't adequate to explain current observations. One line of objection to the theory is that various types of immune system cells *do* interact with "self" in healthy individuals without causing a systemic immune response, much less autoimmune disease or other harmful result. Some of these types of interactions with "self" are even necessary for the proper functioning of regulatory T cells, for example, which suppress the tendency of your immune system to attack you. Another line of objection, which TP considers even more important, is that actually our bodies are filled with microbes that don't harm us, or that are even necessary for our health (e.g. in our gut). These are "non-self" in Burnet's terms, but the body doesn't mount any systemic immune reaction against them. TP considers various ad hoc arguments that have been offered to explain some of these phenomena, such as that certain organs are "immunoprivileged," but shows that they don't hang together -- and that ultimately there isn't any clear criterion for distinguishing "self" from "nonself," other than the circular one of saying that "nonself" is whatever generates an immune reaction. (Disclaimer: throughout this review I'm radically abridging, flattening, and probably distorting, TP's careful arguments.)The book next moves to its constructive argument, advocating a notion of immunity based on the features of molecules and the way in which they are presented: "The continuity theory's central claim is that the triggering of an immune response is due to any strong discontinuity in the expression of antigenic patterns that the organism interacts with, which is to say the sudden appearance in the organism of antigenic patterns strongly different from those with which the immune system continuously (i.e. regularly) interacts. It is thus a matter of a rupture in the continuity of molecular determinants interacting with immune cells." (@137.) The presumption is that the organism (e.g., us) starts as tolerant to a wide range of outside materials, such as bacteria on the surface of food and on our own skins: this had obvious survival benefits when people had to eat food they found in the wild and before they used soap. Subsequently, our immune systems learn to be less tolerant. Nonetheless, rather than having our repertoire of tolerance frozen in infancy, we can develop new tolerances even as adults if we encounter new antigens in small enough quantities and over extended periods of time. TP states the theory broadly enough so that it covers immune response to endogenous materials (e.g., tumor cells and their products) as well as to exogenous ones.TP points out that most antigens will elicit *some* type of immune response, at least at the level of a few cells -- what's of particular interest is understanding what makes a discontinuity big enough to trigger a systemic immune response. To this end TP identifies five types of potential discontinuity: (1) antigen quantities, (2) the speed of antigen appearance, i.e. "dQ/dt", where Q is the quantity of antigen, (3) the degree of molecular difference, (4) the regularity of antigen presentation, and (5) the site of the immune interaction (@144-146). For example, substances in the body undergo changes as the body matures, sometimes due to mutations. But the theory predicts these endogenous substances are unlikely to promote a systemic immune response because they'll usually be similar to substances that have already been presented to the body over a long period, and possibly their build-up will also be fairly slow (factors 2-4). In the latter part of the chapter (Chap. 4), TP also shows how these general principles explain recent observations about immunity in plants and insects, and even

can be applied in the context of RNA interference in bacteria. In chapter 5 TP next shows how continuity theory accounts for the phenomena explained by self-nonself while avoiding its problems and/or simplifying the explanation of the supposed exceptions to that rule. He also shows how it has advantages over several other theories that have been viewed as successors to Burnet's, including the systemic immunity proposal of Niels Jerne and the "danger theory" of Polly Matzinger, among other proposals. As a newcomer to this field I found TP's arguments in Chapters 4 and 5 very cogent, and as a lawyer by training I enjoyed his relentlessness in mustering evidence and logic to chop his way through the alternative theories.Still, the more I thought the discontinuity factors (1) through (5), the less confident I was that I understood how they worked together. Especially, do all five types of discontinuity need to apply before a systemic immune response results? or is just one sufficient? or something in between? Suppose there's a microbe that lives harmlessly in your gut but gets into your eye and starts an infection. It's been presented "regularly" (factor 4), but not in that location (factor 5); similarly, it might have been presented with high dQ/dt (factor 2) only in the eye but not elsewhere. So is the discontinuity in location "first among equals" in determining whether a large-scale immune reaction will occur? Or contrast getting MERS or SARS from someone's sneeze next to you on the train with what happens when you're born, or even what happens when you get off the plane in Kuala Lumpur for the first time after living your whole life in Portland. All these events involve a big dQ/dt of antigens you may never have encountered before. Your exposure after birth or in KL will probably level off after the first big blast -- dQ/dt goes back down to a low value --, so continuity theory predicts you can develop tolerance for most of the antigens; and experience suggests that this is usually what happens. What's different with MERS? A tempting explanation might be that the virus population in your respiratory tract keeps growing (dQ/dt stays big and constant, or increases) -- but the problem is that your body can't know a priori that the level of virus antigen won't *eventually* level off, too. So to mount a systemic immune response it seems that there must be at least one other discontinuity factor at work, such as molecular difference, or a threshold quantity (or concentration) of the virus: in this case TP's factor 2 alone doesn't seem to be sufficient to predict the different outcomes in the various cases. In other words, it seems hard to know what the theory predicts without more explanation about how the factors (1) through (5) interact with each other.In Chapter 6, entitled "What is an Organism?" TP proposes to show that immunology can offer a criterion of individuation, answering the question of "what makes a living thing one discrete and coherent entity" (@227). Note that in TP's usage a "living thing" doesn't include only what we colloquially would call an individual plant, animal or microbe, but also components of it (e.g. cells), aggregates (e.g. a population) and composites (e.g., an insect together with the microbes in its gut).TP proposes the following definition of "organism": "An organism is a functionally integrated whole composed of heterogeneous components that are locally interconnected by strong biochemical interactions and controlled by constant systemic immune interactions of constant average intensity" (@244). In other words, the "organism" that is you includes, among other components, the microbiome of symbiotic and commensal bacteria, etc. in your gut, on your skin, and elsewhere. The boundary of what's "in" and what's "out" of this heterogeneous assemblage is defined by the continuity-based notion of immunity, rather than by, say, a particular DNA sequence, and often it's the whole assemblage that will be what evolution is acting on, i.e an evolutionary individual.To offer an oversimplified example, your ancestor's ability to outrun a rampaging mastodon wasn't just a function of his own DNA, it was also a function of how well the bacteria in his gut allowed him to digest his previous meals. And if he had gotten squashed, then all those bacteria might have eventually died from starvation, too. Since natural selection operates on individuals, we should consider the whole organism, including symbionts and commensals, as the relevant individual in this case. The DNA your ancestor got from his parents wasn't the only DNA on board that individual, so don't believe that your ancestral DNA is sufficient to define you (even ignoring for the moment nucleic acid modifications like the epigenome). In fact, individuals with the same DNA may be very different when it comes to immunity, a fact of significance not only for twins but also for living things like dandelions, of which Richard Dawkins once speculated that there are only four genetic individuals in all of North America (quoted @236).I confess I'm not certain about whether every feature of the continuity theory is necessary to reach a similar evolutionary conclusion. But this is the first time where I've seen a nongenetic definition of a biological individual described so cogently. TP concludes by sketching an argument for how this view of an organism could be extended to unicellular bacteria and archaebacteria, reviving Burnet's early vision of using immunity to characterize individual identity or "self" across all taxonomic kingdoms and phyla.Although TP is a French philosopher, the book reads more like "Anglo-Saxon" analytical philosophy than the often grandiose and/or obscure output of recent Continental philosophers. Not for him provocative and vacuous assertions like "Immunity is a language," an aphorism offered by the Franco-Israeli team of Henri Atlan and Irun Cohen, and dissolved by TP with more courtesy and self-restraint than I could have mustered if I had his expertise (@188-190). TP writes in a clear, no-nonsense style, helped by a good translation from Elizabeth Vitanza, and concretely grounded in references to experimental, observational and clinical evidence. As a bonus, this is probably the only book of any type of theory I've read in the past few years from which the names Foucault, Latour, Deleuze and Lacan are all (refreshingly) absent. At the same time, since he's a philosopher rather than a laboratory scientist, it's possible that TP's theory won't have the impact among biologists and the medical community that it deserves. Which would be a pity, because if TP is right you'd think that future therapies would be

designed differently, e.g. to be more respectful of microbiomes and more cautious about possible adverse endogenous effects.In sum, it could be of both practical and philosophical significance if TP is right, but we'll have to wait to see if further experiments and observations bear him out. In the meantime, this book provides a very stimulating immersion in the philosophy of biology, even for a curious amateur.

What counts as an individual in the living world? What does it mean for a living thing to remain the same through time, while constantly changing? These questions are the province of immunology, one of the most dynamic fields in biology. Immunology answers these questions with its theory of "self" and "nonself" which has dominated the field since the 1940s. Thomas Pradeu argues that this theory is inadequate, because immune responses to self constituents and immune tolerance of foreign entities are the rule, not the exception. Instead Pradeu advances an alternative theory, the continuity theory, which offers a new way to answer the question of what triggers an immune response. It also echoes the recent realization that all organisms, and not only higher vertebrates, have an immune system. Pradeu's main thesis is that the self-nonself theory should be abandoned, but that immunology still proves to be decisive for delineating the boundaries of the organism. Articulating an evolutionary and an immunological perspective, he offers an original conception of the organism. Tolerance of the fetus by the mother and of countless bacteria on the body's surfaces proves that every organism is heterogeneous, that is, made of entities of different origins. In other words, every organism appears as a chimera , a mixed living thing-the cohesiveness of which is ensured by the constant action of its immune system. The Limits of the Self, will be essential reading for anyone interested in the definition of biological individuality and the understanding of the immune system.

"Thomas Pradeu's The Limits of the Self represents a sophisticated analysis of how the self can be defined in terms of the immune system and how this strictly biological view can inform the philosophical concept. ... Thomas Pradeu's Continuity Theory is arguably the clearest alternative to Burnet's self/non-self model" (Richard P. Novick, The Times Literary Supplement, Feb 15, 2013)From the Back Cover"The topic and the thesis of this book are both of great philosophical interest and practical significance. Some of the most important medical questions, most obviously around cancer and the action of pathogens, are being transformed by contemporary molecular biology. But these developments cannot be properly understood without an adequate conception of the immune system the failure of which is a basic assumption of our interpretation of these pathologies. Philosophical discussions of immunology are few and far between; but if anyone thought this was because the topic was philosophically uninteresting, this book will change their minds. The dynamic conception of the immune system that Pradeu proposes has vital implications for the meaning of health and illness and even for our conception of the organism. It should be widely discussed by philosophers of biology, but also by the biomedical scientists whose work it addresses."- John Dupre,UniversityofExeter.About the AuthorThomas Pradeu is Associate Professor in Philosophy of Science at Paris-Sorbonne University, and Associated Researcher at IHPST Paris. His research deals mainly with the definition of the organism, the notion of biological individuality, and the concept of "self" as it appears in today's immunology. He was trained both in philosophy (Ecole normale superieure of Paris and Pantheon-Sorbonne University) and in immunology(Ecole normale superieure of Paris and Harvard University). In his research, he is interested in exploring key immunological concepts and theories.His publications are to be found in scientific (Science, PNAS), medical (Lancet), and philosophical (Biology and Philosophy) journals.