THOMAS PRADEU

# *The Limits of the Self*

## IMMUNOLOGY AND BIOLOGICAL IDENTITY

# THE LIMITS OF THE SELF

## Immunology and Biological Identity

Thomas Pradeu

TRANSLATED FROM FRENCH BY

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OXFORD
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Oxford University Press, Inc., publishes works that further
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Published by Oxford University Press, Inc.
198 Madison Avenue, New York, New York 10016
www.oup.com



Library of Congress Cataloging-in-Publication Data
Pradeu, Thomas.
The limits of the self : immunology and biological identity / Thomas Pradeu.
p. cm.
ISBN 978-0-19-977528-6 (alk. paper)
1. Immune system. 2. Immunology—Philosophy. 3. Self (Philosophy) I. Title.
QR181.P64 2012
616.07'9—dc23
2011023261

1 3 5 7 9 8 6 4 2
Printed in the United States of America
on acid-free paper

# ACKNOWLEDGMENTS

I would like to thank for their help and support Samuel Alizon, Eric Bapteste, Anouk Barberousse, Cédric Brun, Richard Burian, Edgardo D. Carosella, Stéphane Chauvier, Hannah-Louise Clark, Jacques Dubucs, François Duchesneau, John Dupré, Melinda Fagan, Jean Gayon, Charles Girard, Peter Godfrey-Smith, Alexandre Guay, Philippe Huneman, Richard Lewontin, Marie-Claude Lorne (who was tragically lost in 2008), Michel Morange, Anne Marie Moulin, Maureen O'Malley, Susan Oyama, Jan Sapp, Arthur Silverstein, Kim Sterelny, Alfred Tauber, Mireille Viguier, and Charles Wolfe.

Edgardo D. Carosella, Stéphane Chauvier, Hannah-Louise Clark, Ellen Clarke, François Duchesneau, Jean Gayon, Peter Godfrey-Smith, Richard Lewontin, Michel Morange, Elliott Sober, and Alain Trautmann kindly accepted to read carefully one or several chapters of this book and made very helpful comments. I want to thank them warmly.

In addition, I was very much helped by exchanges with Edwin Cooper, Anthony de Tomaso, Gérard Eberl, Eugene Koonin, Roger Innes, Shimon Sakaguchi, and Lisa Steiner.

Special thanks to Richard Lewontin and Susan Oyama, as well as to Scott Gilbert, in whose ideas I immediately felt "at home." I hope that they will see themselves reflected a bit in this immunological mirror. I also want to thank my university, Paris-Sorbonne University, and the Institut d'Histoire et de Philosophie des Sciences et des Techniques (IHPST) in Paris, which is an extraordinary place for doing research.

Peter Ohlin at Oxford University Press has been an outstanding editor, always open to my questions or suggestions.

And finally, thank you, Magali and Camille.

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# INTRODUCTION

Can two individuals that are said to be "identical"—twins, for example—nevertheless be distinguished from one another? Where does a colonial organism, such as a sea coral, begin and end? Is such a colonial organism one or several individuals? What ensures that the larva is the "same" living thing as the adult fly it becomes despite the considerable changes it undergoes? All of these questions form a more general problem: What makes the identity of a living thing? This problem of the definition of biological identity is the one I put forth in this book. Once I have defined the problem, I will show why one discipline among the modern life sciences, immunology, has made the study of this question of biological identity its own domain.

## WHAT IS BIOLOGICAL IDENTITY?

The question "What makes X's identity?" can be asked of any entity, even inert objects. Here, the focus is on living things: "What makes the identity of a living thing?" In reality, to ask what makes the identity of a living being is to ask two questions: on the one hand, what

makes the *uniqueness* of a living thing, and on the other, what makes its *individuality*. The first question, that of uniqueness, is the following: What makes a living thing different from all other living things, including those that belong to the same species? For example, are there means of distinguishing between two identical twins? Or between an organism and its "double" created through cloning? The second question, that of individuality, is: What counts as *one* living being? In other words, what constitutes a discrete, cohesive, clearly delineated unit in the living world? The problem of individuation is effectively a problem of separation, or delineation, of the real: it consists of knowing how to determine the *boundaries* of the entities being described. It is the problem that is sometimes referred to as that of the "furniture of the world" (what counts as *one* thing, as *one* entity?), applied, in this case, to living things. At least in the domain of the living, an individual is never strictly indivisible—contrary to the etymology of the term "individual." As a result, to understand what creates the unity of a living being consists of determining how it is the unity of a plurality, which is to say why, although it is formed of diverse partially isolatable constituents, the organism is still a unified whole. It is possible, for instance, to wonder what counts as "one" individual in a coral reef: Is a coral one single vast individual whose polyps (each little "tube" topped with a mouth and tentacles) are so many "parts," or should each polyp be considered an "individual"? This example reveals that what biological individuation aims is to offer criteria that allow us to determine precisely what the boundaries of a living being are.

Although they are often confused, uniqueness and individuality are quite distinct from each other: two entities are individuals as soon as it is possible to say that they are two. This does not assume that each entity must necessarily be considered unique. Two tables that would be perfectly identical would not, by definition, be unique; however, they would in fact be two individuals since they could be

distinguished and counted as two entities. The same is true of two living things that would be identical while still existing as two separate beings. Thus, the question of biological uniqueness and the question of biological individuality must be distinguished from one another. Of course we could, with Leibniz, affirm that two entities are never completely identical, that they are always unique from a certain number of perspectives. However, in practice, there are entities that we wish to qualify as "identical," particularly in biology: think, for example, of each clone in a clonal plant. The question of biological uniqueness must not then be considered already settled; on the contrary, to answer it requires the establishment of biologically pertinent criteria.

The issue of biological identity, in particular the dimension of biological individuality, is one of the most hotly debated among biologists (Ghiselin 1974; Buss 1987; Maynard-Smith and Szathmary 1995; Michod 1999; Santelices 1999; Queller 2000; Gould 2002; Gardner and Grafen 2009; Queller and Strassmann 2009; Folse and Roughgarden 2010) and philosophers of biology (Hull 1978, 1992; Wilson 1999; Sober 2000; Okasha 2006; Godfrey-Smith 2009). The current literature on levels of individuality and the transitions between these different levels is staggering (e.g., Maynard-Smith and Szathmary 1995; Michod 1999; Queller 2000; Okasha 2006; Godfrey-Smith 2009). The question of biological identity has also been asked by numerous philosophers past and present (Aristotle 1984a, 1984b; Locke [1690] 1979; Leibniz [1765] 1996; Reichenbach [1928] 1958; Strawson 1959; Wiggins 2001). For them, the living being, or rather a certain type of living being, namely an organism, has served as the typical example of what counts as an individual, and, by extension, as the typical example of an entity whose identity can be studied. For Aristotle, in particular, the usual examples of primary substances are the individual man or the individual horse—examples taken up again literally by Wiggins (2001).

The conceptual distinctions that I have proposed are standard in the domain of ontology. However, they are rarely formulated with precision with regard to living beings. My goal is to apply the ontological question "What makes a being's identity?" to the living world, asking "What makes a being's identity in the living world?" The following two questions lie at the heart of this book: First, what counts as an individual in the living world? And second, is each living being unique, and if so what ensures this uniqueness?

One of the branches of contemporary biology, immunology, considers these questions its province. At the heart of immunology, traditionally defined as the science that studies an organism's defense against any foreign entity capable of invading it, have lain the notions of "self" and "nonself" since the 1950s. In setting out to scientifically define the two terms "self" and "nonself," immunologists claim to respond both to the problem of the uniqueness of each living thing and to the problem of its individuality. One of the principal objectives of this book is to establish the precise meaning of these two notions of "self" and "nonself" in order to determine whether they effectively constitute a proper foundation for a definition of biological identity.

## THE IDENTITY OF THE LIVING BEING: A CENTRAL QUESTION OF IMMUNOLOGY

### *From "Self" to Identity*

What allows immunologists to lay claim to the problem of biological identity? To answer this question, it is necessary to understand the meaning of the concepts of "self" and "nonself." The self is that which is specific to the organism, that is, both that which defines it and that which uniquely belongs to it. The nonself is everything that is not the self, or what differs from the self's content. For example, in the case of a transplant in an animal, a graft of an organism onto

itself ("autograft") is tolerated, whereas a graft from a donor organism onto another ("allograft") is, in almost all cases, rejected. Thus, starting in 1949, Australian virologist Frank Macfarlane Burnet (1899–1985) suggested, drawing specifically on transplantation experiments, to conceive of immunity with the vocabulary of "self" and "nonself" (or "not-self," in Burnet's own words) (Burnet and Fenner 1949). Today, immunologists accept that an organism is capable of an immunological recognition of self and nonself. This distinction between self and nonself allows the organism to trigger a defensive response against all *foreign* entities—which is to say anything different from the self, whereas it will not attack, except for in pathological cases, anything belonging to its self. As Burnet (1941: 60) writes: "There can be little doubt that the whole subject matter of immunology is founded on this intolerance of living matter for foreign matter." As for immunologist Jean Hamburger (1978: 28), he affirms: "Within the same animal species... apart from identical twins, no two individuals are exactly alike.... Each individual is able to recognize another individual of the same species as different from himself.... Having identified the allografted tissue as foreign, he destroys and eliminates it, while he recognizes fragments of his own body as his own and does not reject them."

What the "nonself" means to the organism, then, is any foreign body that might penetrate it. It can be pathogens (bacteria, viruses, fungi, helminthes, etc.), as well as a graft. In 1949, Burnet and Fenner talked only about "self-markers," but over time the "self-nonself theory" was elaborated to interpret immune reactions from these two central concepts of self and nonself. This theory has dominated immunology for the past sixty years. According to its proponents, the study of the immune system shows that every living being knows its own identity and defends it against any outside threat: it would be able to distinguish between its own components

and any foreign one, and would eliminate any foreign body that would penetrate it. Hence, the understanding of biological identity would be immunology's essential and distinctive objective. Indeed, Jan Klein (1982) called it "the science of self/nonself discrimination"; in his Nobel lecture, Jean Dausset claimed that the system of histocompatibility created the organism's "ID card," which was monitored nonstop by the immune system (Dausset 1981); even Alfred Tauber (2009), who has quite critically analyzed the use of the terms "self" and "nonself" in immunology, argues that immunology is concerned with defining the characteristics of identity that allow one to make the distinction between two individual organisms (along with the question of "describing the mechanisms that defend organisms from their predators"). The recognition of self and nonself by the immune system would therefore make biological identity a question to which immunology could respond. I now turn to how immunology answers, or tries to answer, the twofold question of uniqueness and of individuality in the living being.

## *Immunology and the Uniqueness of the Living Being*

Immunology has appropriated the question of biological uniqueness by integrating and elaborating on the results of genetics. Genetics demonstrates that, in the case of sexual reproduction, two living beings—with the exception of identical twins—are always different, which amounts to saying that every living thing is genetically unique. As for immunology, it furthers this line of research by asking the question of uniqueness at two levels. The first is the immunogenetic level: there is a great diversity in genes involved in immunity, as well as numerous processes of genetic variation and recombination—so much so that, based on a limited number of genes, it is possible to create a huge number of different immune receptors. Moreover, the polymorphism of major histocompatibility complex

(MHC) genes—often called "HLA" for *Human Leukocyte Antigens* in humans—is considerable. The second level is phenotypic: it is expressed in the diversity of immune receptors and the molecules of the histocompatibility system. In mammals, in particular, proteins involved in immunity, especially immunoglobulins, T cell receptors, and MHC molecules, demonstrate an extremely high degree of phenotypic diversity. In humans, for instance, an estimated $5x10^{13}$ different immunoglobulins and $10^{18}$ T cell receptors potentially exist. Immune components are therefore one of the most convincing manifestations of each organism's uniqueness, matched only by the phenotypic diversity expressed in the nervous system. In other words, the immune phenotypic characteristics are one of the best ways to distinguish between two individuals or to biologically single out an individual. Dausset (1990: 27) thus says of the HLA system: "The HLA system is the best definition of the being in relation to another individual of the same species, since the experience of transplantation shows us that it is the greatest barrier."

One very important aspect of the phenotypic expression of uniqueness is the construction of a being's uniqueness over the course of time: immune receptors of B and T cells are produced in relation to antigens the organism encounters by virtue of the "immune memory" mechanism. By this mechanism, an organism that reacts to an antigen, for example a bacterium, produces immune receptors specific to that bacterium, then maintains these receptors for its entire life, and will respond more quickly and more efficiently should the same antigen ever be reintroduced. The immune system is consequently said to make an important contribution to the diachronic uniqueness of the living being just as the nervous system does: my immune "self" makes me a unique individual with regard to all other living beings, including those of my own species. Indeed, even two monozygotic twins are different from the perspective of their immune systems.

### *Immunology and Individuality*

Immunology attempts to clarify the question of a living being's individuality by showing that its boundaries are drawn by its immune system, which constantly monitors its components and eliminates everything that is different from itself. It follows that the immune system would be based on the knowledge of self-components and would allow maintenance of the living being's identity by the rejection of any exogenous or foreign entity, in particular pathogens. The immune system would define each living being's individuality and would guarantee the maintenance of its identity over time, what one may call, with Burnet (1962), the "maintaining of integrity." The immune system would assure that *one* being is dealt with and would preserve the unity of this being through time.

The dimension of individuality converges with the dimension of uniqueness in the developments of the transplantation field in the first half of the twentieth century. In showing the acceptance of autografts and grafts from identical twins, transplantation allowed for a precise definition of the expression of individuality in organisms, making this question a fundamental issue of immunology (Loeb 1930, 1945; Medawar 1957; Hamburger 1976).

## CONFLICT BETWEEN IMMUNOLOGY AND OTHER BIOLOGICAL FIELDS ON THE QUESTION OF BIOLOGICAL IDENTITY

Immunologists therefore rely on apparently solid experimental arguments when they claim that they are dealing with the identity of the living being in the double sense of its uniqueness and its

individuality. It appears highly unlikely, however, that immunology could be the *only* biological discipline capable of tackling this problem. For instance, the question of uniqueness seems to pertain much more to genetics than to immunology: the uniqueness of sexually reproducing organisms is first and foremost genetic in origin. Immunologists certainly put forth immunogenetic and phenotypic arguments in order to say that each living being's uniqueness is even larger than that which can be ascertained by genetics, but in these circumstances it would be much exaggerated for them to claim the question of biological uniqueness as theirs alone.

As for the question of individuality, if it has been at the center of numerous biological and philosophical debates for the past thirty years, it has been so almost exclusively from the perspective of evolution (Ghiselin 1974; Hull 1978; Buss 1987; Maynard-Smith and Szathmary 1995; Michod 1999; Santelices 1999; Queller 2000; Gould 2002; Okasha 2006; Gardner and Grafen 2009; Godfrey-Smith 2009; Queller and Strassmann 2009; Folse and Roughgarden 2010). The theory of evolution by natural selection provides a response to the question of biological individuation by defining a hierarchy of "evolutionary individuals," that is, entities upon which natural selection acts (Lewontin 1970; Hull 1978; Buss 1987; Gould 2002; Okasha 2006; Godfrey-Smith 2009). In this hierarchy, the organism appears only as one of several possible biological individuals, along with the gene, the genome, the cell, or even the group, the species, etc. As a result, it seems difficult for immunology to consider that it alone can respond to the question of biological individuality.

Immunology must therefore take into account other biological disciplines that also claim to clarify the question of biological identity. It will be critical, in this book, to determine what relation immunological discourse supports with these other disciplines:

Are they complementary or conflicting approaches? Or do they perhaps envision different objects, and do not mean the same thing when they resort to the terms "uniqueness" and "individuality"?

## THE PROBLEM OF SCALE WHEN DETERMINING BIOLOGICAL IDENTITY

The confrontation that I have just briefly sketched out between immunology and evolutionary biology on the question of individuation brings up another important concern: What is the scope of this notion of biological identity? In effect, individuation as explained by the theory of evolution appears to apply to the entire hierarchy of living beings (genes, cells, organisms, etc.), whereas individuation as explained by immunology only seems to concern itself at the level of the organism. Yet nothing indicates that the question of the living being's identity must be asked exclusively at the level of the organism.

Even if we admitted that the problem of biological identity arises at the level of an organism and not at other biological levels, a crucial issue would remain: With exactly which organisms is immunology concerned? In order for immunology to offer a general conception of what makes the identity of an individual organism, it would be necessary for it to apply to all organisms, or at least to the great majority of them. Now, for Burnet, the founder of the self-nonself theory, immunology applies exclusively to higher vertebrates, as he thought that they only had a true "immune system." If Burnet is right, therefore, immunology cannot claim to shed light on the question of a living being's identity except for a tiny fraction of living things. This would put immunology at a considerable disadvantage compared with evolutionary biology, which deals with numerous levels of life.