1 Introduction: The Centrality of Immunity in Biology and Medicine

Immunology is one of the most central and dynamic fields of today's biological and biomedical sciences. It constitutes, in fact, a pivotal bridge between basic biology and medicine. Immunology is generally defined as the domain studying the defense of the organism against pathogens but its scope is actually much wider. Topics as diverse as cancer, infectious diseases, vaccination, transplantation, autoimmune diseases, chronic inflammatory diseases, metabolic diseases, development, aging, repair and regeneration, and host–microbiota interactions, among many others, are all directly related to the field of immunology. Furthermore, it now appears that immune systems exist almost ubiquitously across the living world (including in animals, plants, and prokaryotes). In fact, virtually all domains of biology and medicine are connected to immunology, and when opening recent issues of leading science or medicine journals, one can get the impression that immunology is omnipresent. Why has immunology become so central in our science and daily lives – and why does this matter philosophically?

I work as a philosopher of science embedded in an immunology lab affiliated with the Bordeaux University hospital. Over the years I have become increasingly aware of the key role played by the immune system in practically all kinds of diseases – in their aetiology, diagnosis, and treatment. If you receive a transplant, the biggest challenge is immunological rejection of the graft, which explains why you will be prescribed immunosuppressive drugs. If you have cancer, depending on the type of tumor, you might receive one of the now hugely discussed immunotherapies, an advance that was awarded the 2018 Nobel Prize in Physiology/Medicine and which constitutes an immense hope for medical doctors and patients worldwide (Ribas and Wolchok 2018). Even if you do not receive immunotherapies, the number of the different populations of your immune cells will be checked regularly to choose and adapt your treatment. Immunology is also central, naturally, for our understanding of autoimmune diseases: in type 1 diabetes, for instance, immunologists seek to explain why the immune system selectively destroys pancreatic β-cells (which secrete insulin), and how this process might be controlled (Lehuen et al. 2010). If you happen to come back from another country with a bad viral or bacterial infection, again, the main goal of medical doctors will be to make your immune system cope with that infectious agent without severely disturbing the balance of your immune responses to other elements. Moreover, vaccination rests on the idea of stimulating the immune system against a particular target. The immune system also plays a major role in pathologies as diverse as cardiovascular

diseases (Hansson and Hermansson 2011), neurodegenerative disorders (Heneka et al. 2014; Heppner et al. 2015), and obesity (Lumeng and Saltiel 2011) – and for all these diseases it constitutes one important point of leverage used in the clinic.

So, immunology is pretty much unavoidable in our daily lives, both in health and disease. One aim of this Element is to show that immunology is also of paramount importance for philosophers. The most central contribution of immunology to philosophy concerns, arguably, the understanding of biological individuality. From the end of the nineteenth century onward, it has been recognized that immunology raises key questions about what a biological individual is, what makes it unique, how its boundaries are established, and what ensures its identity through time (Tauber 1994; Pradeu 2012). This Element will explore other philosophical lessons that can be drawn from current immunology – including the definition of life (or, more specifically, the basic requirements for all living things), the delineation and regulation of bodily systems, part–whole relations, the notion of biological function, and mind–body interactions.

The main claims made in this Element are summed up in Box 1.1.

The present philosophical exploration of immunology will be made through the examination of concrete scientific and medical examples, such as host–microbe symbioses, cancer immunotherapies, and the CRISPR-Cas systems.

Box 1.1 Main Claims Made in the Present Element

1. Most (perhaps all) living things possess an immune system.
2. Immunity is not limited to the activity of defense. The immune system plays a central role in activities as diverse as development, tissue repair, and clearance of debris, among others.
3. Anyone interested in biological individuality must take into account what immunology says on this question.
4. The immune system plays a key role in delineating (and constantly redrawing) the boundaries of a biological individual, determining which elements can be part of that individual, and insuring its cohesion.
5. Cancer results from a process of decohesion in a multicellular organism, and the immune system has a major influence on the control of this process.
6. The nervous system and the immune system intimately interact. Neuroimmunologists' claims that the immune system can influence behavior and even cognition are worth examining.

This Element tries to talk simultaneously to philosophers, scientists, and medical doctors. To philosophers of biology, this Element says that immunology raises many crucial conceptual and philosophical issues and can integrate elements coming from several related biological fields, including microbiology, developmental biology, physiology, evolution, and ecology. For philosophers and metaphysicians, this Element argues that immunology can shed new light on some philosophical questions that have been fundamental since at least the time of Aristotle, such as what constitutes the identity of an individual through time. The message to biologists is that the immune system must be rethought as one of the most basic and indispensable aspects of any living thing. Finally, the suggestion to medical doctors is that a constant reflection on immunological concepts can help open up novel therapeutic avenues – for instance, about cancer, autoimmune diseases, or the management of ecological interactions between microbes within our bodies. Overall, the approach taken in this Element will be an example of philosophy *in* science, that is, a type of philosophical work that aims at interacting intimately with science and contributing to science itself (Laplane et al. 2019).

The contents of the Element are as follows. Section 2 critiques the idea that immunity should be defined exclusively in light of the concept of defense of the organism against external threats and extends immunity to other key dimensions, particularly development, repair, and other housekeeping activities. Section 3 shows that immunology is central to the definition of biological individuality and proposes that a physiological individual is a community of heterogeneous constituents, including microbes, unified by the action of the immune system. Section 4 examines the claim that cancer can be defined as a breakdown of biological individuality and argues that the immune system can both prevent and promote this breakdown. Finally, Section 5 explores the interactions between the nervous system and the immune system and assesses the claim that the immune system may be involved in behavior and cognition.

2 Immunity: A Matter of Defense?

If you cut yourself with unclean tools while doing some gardening, the pervasive bacterium *Staphylococcus aureus* might enter into your body via the wound site. If your immune system works normally, you will certainly get rid of these bacteria rapidly. An oversimplified description of this process is that tissue-resident cells, especially macrophages, detect the bacteria, trigger a local inflammation (which facilitates the immune response), and usually eliminate the bacteria, sometimes with the help of other innate immune cells (like neutrophils) that are recruited at the site of infection. If the bacteria are not

promptly eliminated, then antigen-presenting cells, typically dendritic cells, migrate to secondary lymphoid organs such as lymph nodes and present bacterial fragments to naive lymphocytes circulating in these compartments. Lymphocytes with high specificity and affinity for these bacterial antigens are activated, and their populations expand. Specific lymphocytes then migrate to the infection site, and, in concert with many other cellular and molecular components such as antibodies, they destroy the bacteria.

The highly intertwined processes that collectively constitute an immune response suggest that our immune system is truly a system – a set of processes that involve many interacting cells distributed throughout the body. Indeed, although it comprises particular cells (Box 2.1) and organs, the immune system exerts its influence everywhere in the organism, especially via its network of lymphatic vessels and its numerous tissue-resident cells (Figure 2.1).

The system by which an organism defends itself against pathogens is precisely what has generally been called the *immune system* (Janeway 2001; Paul 2015). Is the activity of the immune system, though, only a matter of defense? In this section, I show that immunity has been understood historically as an organism's capacity to defend itself against pathogens, and that defensive immune mechanisms have been identified in all species. I then argue that the immune system cannot be reduced to its defense activity and promote on this basis an extended view of immunity. Next, I explore the complexities of accounting for the evolution of immunological processes and attributing a single function to the immune system. Finally, I explain why it is difficult in today's immunology to offer a definition of immunity.

Box 2.1 Simplified Presentation of the Main Cellular and Molecular Components of the Immune System in Mammals, with Some of Their Activities

1 Cells

Macrophages: phagocytosis, elimination of pathogens, clearance of debris, antigen presentation, tissue repair.
Neutrophils: phagocytosis, elimination of pathogens, chemotaxis, constitution of neutrophil extracellular traps, tissue repair.
Mast cells: elimination of pathogens, wound healing, immune tolerance.
Dendritic cells: antigen uptake at the periphery, antigen presentation in secondary lymphoid organs.
Natural killer cells: elimination of infected cells and cancer cells.
Innate lymphoid cells: elimination of pathogens, tumor surveillance, tissue repair, metabolism.

Effector T lymphocytes: stimulation of other immune cells, destruction of infected cells.
Regulatory T lymphocytes: downregulation of other immune cells, prevention of autoimmune diseases.
B *lymphocytes*: neutralization, opsonization (promotion of phagocytosis), complement activation.

2 Molecules

Complement: phagocytosis, inflammation, membrane attack.
Cytokines, including chemokines, interferons, and interleukins: cell signaling.

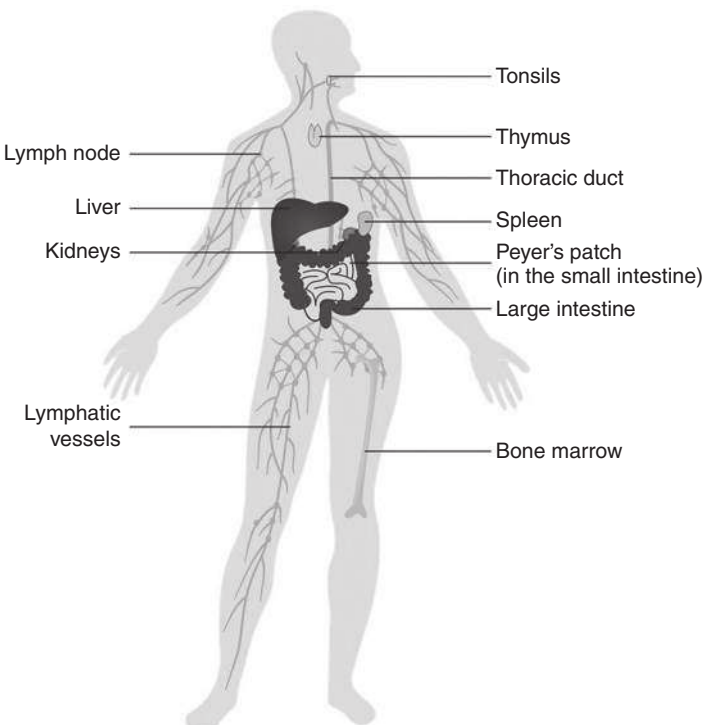

Figure 2.1 Human immune system. The human immune system, which comprises different organs (thymus, bone marrow, spleen, lymph nodes, and so on), different cells (both circulating and resident) and molecules, and a network of lymphatic vessels, exerts its influence everywhere in the organism. (Figure drawn by Wiebke Bretting).

2.1 Historically, Immunity Has Been Understood As the Capacity of an Organism to Defend Itself against Pathogens

Pathogens have constituted a major force shaping the evolution of human beings throughout their history. Devastating infectious diseases are a clear example. Plague, caused by the bacterium *Yersinia pestis*, killed more than 50 million people in the fourteenth century. More recently, the pandemic of influenza virus following the First World War killed over 40 million people worldwide.

It has long been recognized that humans can resist some infections, with important differences between individuals and/or populations. While some people are killed, others show disease symptoms but survive, and still others do not seem to be affected at all. The notion of immunity is meant to capture this idea of a specific capacity to avoid the detrimental effects of a pathogen. Immunity is generally defined as the capacity by which an organism can defend itself against pathogens.

Host–pathogen interactions are complex, as each partner adapts to the other. This emphasizes the need to always understand immune defense and pathogenicity in their ecological and evolutionary contexts (Box 2.2).

Box 2.2 Importance of the Ecological and Evolutionary Context When Discussing Immune Defense and Pathogenicity

Immune defense and pathogenicity are not intrinsic properties of hosts and microbes. Rather, they are a matter of evolutionary and ecological context. Approaches that pay attention to evolution and ecology have historically played an important role in immunology (Burnet 1940; Méthot and Alizon 2014). They have taught three important lessons.

1 Pathogenicity Is a Gradual and Contextual Phenomenon

An infectious microorganism is not intrinsically pathogenic (Casadevall and Pirofski 1999; Méthot and Alizon 2014): it can be harmful in one species and benign in another, and its virulence often varies between different individuals in a population. Even within an individual, pathogenicity depends on pathogen localization, host physiological and immunological state at the moment of the infection, the presence of other microorganisms, and the past interactions with this pathogen or others, among many other factors. In addition, the vast majority of microorganisms are not harmful to their hosts.

2 An Ever-Going "Arms Race" Occurs between Hosts and Pathogens

Hosts and invaders continuously adapt one to the other. This constitutes one of the main reasons why immune systems are so intricate, with so many different components acting at various levels. Often, a pathogen evolves a way to evade a given recognition system of its host species, but then the host species evolves new recognition systems, which in turn might be circumvented by the pathogen. Such host–pathogen competition often takes the form of manipulation of the immune system by pathogens (Finlay and McFadden 2006). For example, various bacteria display molecular patterns that look like those of the host (molecular mimicry). Furthermore, some bacteria can establish residence within immune cells, which enables them to partly escape the immune response – as *Mycobacterium tuberculosis* does in macrophages, for instance.

3 Immune Defense Comes at a Cost

As emphasized by the recent field of ecological immunology (or ecoimmunology (Schulenburg et al. 2009)), immune responses are costly because the immune system takes up many bodily resources, and if things go wrong, these responses can cause terrible damage to the organism. Ecological immunology has also shown the existence of trade-offs between the different physiological responses of a host to various environmental challenges, for example, between immunity, reproduction, growth, and thermoregulation (Schulenburg et al. 2009).

Historically, the definition of immunity as defense against pathogens is intimately connected with the development of the vaccination technique (Moulin 1991; Silverstein 2009). The birth of immunology as a biomedical field was related with the process of so-called immunization, that is, the acquisition of protection against a specific agent. Etymologically, immunity means an exemption (the right to legally escape specific taxes in ancient Rome). The development of large-scale scientific vaccinations, particularly with Robert Koch and Louis Pasteur in the nineteenth century, is often seen as one of the main foundations of the field of immunology (Bazin 2011). Vaccination is connected with the idea that an organism can increase its defense capacity by "learning" how to neutralize a given pathogen. The vaccinated organism responds quicker and more strongly if it reenters into contact with the same pathogen. This capacity is called *immunological memory*, a phenomenon that

Box 2.3 The Distinction between Innate and Adaptive Immunity and Its Limits

Immunologists often distinguish between innate and adaptive immunity: innate immunity is supposed to correspond to a quick immune response, without training, whereas adaptive immunity takes more time and entails the capacity to "learn" from previous encounters with a given target. (A more precise definition says that innate immunity is characterized by germline-encoded receptors, while adaptive immunity is characterized by the production of novel immune receptors via somatic recombination and clonal expansion (e.g., Lanier and Sun 2009).) Innate and adaptive immunity, however, intimately and dynamically interact. Furthermore, over the last two decades the distinction between them has blurred because many immune components can be located on a gradient from innate to adaptive immunity (Flajnik and Du Pasquier 2004), and immunological memory is in fact a complex, multidimensional, and gradual process found across the living world, including in bacteria and archaea (Pradeu and Du Pasquier 2018).

has long been used to make a distinction between two arms of immunity, namely innate and adaptive immunity (Box 2.3).

2.2 Defensive Immune Mechanisms Have Been Identified in Virtually All Living Things

Beyond humans, all animals, plants, unicellular eukaryotes, bacteria, and archaea are constantly under the potential threat of pathogens and have evolved multiple mechanisms to cope with those pathogens (Anderson and May 1982; Stearns and Koella 2008). Contrary to the long-held view that only vertebrates possess an immune system, in the last thirty years or so immune systems have been found in all the species in which their presence has been thoroughly investigated (Pradeu 2012). Importantly, one can observe that, in all these cases, the criterion used for saying that an immune system exists in a species has been the identification of a system of recognition, control, and elimination of pathogens. This confirms that defense remains the intrinsic, if sometimes implicit, definition of immunity that most biologists adopt when they talk about the immune system.

Plants lack a circulatory system and mobile immune cells, but they are capable of establishing immune responses that are highly specific, with limited damage to the host, and that can even generate a form of immunological memory (Spoel and Dong 2012). Plants deal with pathogens by diverse

modes of recognition (including nucleotide-binding domain, leucine-rich repeat (NLR) receptors) and effector responses (Jones and Dangl 2006).

Bacteria and archaea can be infected by pathogens, including viruses called *bacteriophages*, or more simply *phages*. They respond to these pathogens through different immune mechanisms, including suppression of phage adsorption, restriction modification of the invading phage genome, abortive infection, and the recently discovered CRISPR-Cas systems (CRISPR stands for "**C**lustered, **R**egularly **I**nterspaced, **S**hort **P**alindromic **R**epeats") (Hille et al. 2018). CRISPR-Cas systems provide many bacteria and archaea with protection against phages and other mobile elements (including plasmids and transposons) through a three-step process. The first step is adaptation: small fragments of DNA from the invader are incorporated into the CRISPR array of the host. The second step is expression and processing: the CRISPR array is transcribed, and the precursor transcript is processed to generate CRISPR RNAs. The final step is interference: the CRISPR RNA guides a complex of Cas proteins to the matching target, which initiates the destruction of the invading nucleic acid (Jackson et al. 2017). CRISPR-Cas has generally been described as a key defense mechanism of prokaryotes against mobile elements (including phages) (Horvath and Barrangou 2010), along with other, more recently identified antiphage defense systems (Doron et al. 2018). Most experts even consider CRISPR-Cas as a form of *adaptive* immunity in bacteria and archaea (because it displays a form of immunological memory) on top of being heritable, as it can be transmitted to daughter cells (Horvath and Barrangou 2010; Hille et al. 2018). This has led to discussions over the potentially Lamarckian nature of the CRISPR-Cas system (see (Koonin 2019) and accompanying commentaries).

Other important examples of organisms with now well-described immune systems include insects (Lemaitre and Hoffmann 2007), sponges, hydra, and slime molds (Müller 2003; Chen et al. 2007; Augustin et al. 2010).

2.3 Extended Immunity: Immunity Goes Well Beyond Defense

The centrality of host defense against pathogens in the survival of all organisms should not obscure the fact that immunity goes well beyond mere defense. Although immunity was long conceived exclusively as a system of defense, recent research has shown that immune processes actually play a critical role in a wide variety of physiological phenomena such as development, tissue repair, clearance of debris or dead cells, maintenance of local tissue functions, metabolism, thermogenesis, and the functioning of the nervous system, among many others (Pradeu 2012; Rankin and Artis 2018), leading to an extended view of immunity. Repair is a particularly fundamental process, which maintains the integrity and cohesion of the organism.

When you cut yourself, in addition to the well-known action of platelets, which initiate blood clot and vasculature closure, a horde of immune cells is required at every stage of the repair process to insure proper wound healing (Gurtner et al. 2008; Wynn and Vannella 2016). The three key stages are inflammation, new tissue formation, and remodeling. The main immune cells participating in tissue repair are neutrophils and macrophages. The plasticity and adaptation to context of these cells are crucial (Laurent et al. 2017). Immune cells are also important in processes of regeneration, such as those found in plants, hydra, arthropods, and amphibians, and by which entire complex structures such as limbs can regrow (Eming et al. 2014). Another key daily activity of the immune system is the clearance of bodily debris, coordinated by phagocytotic cells (Nagata 2018). In addition, the immune system is essential for development, that is, the early construction of the organism. This includes the indispensable role of immune-mediated apoptosis and phagocytosis very early on in many developmental processes (Wynn et al. 2013; Okabe and Medzhitov 2016), as well as the role of the complement in development (Ricklin et al. 2010; Stephan et al. 2012) (e.g., phagocytosis mediates the indispensable elimination of excessive tissues; the complement, a cascade of proteins in the blood, remodels synaptic connections in the developing nervous system). Importantly, even though the above description applies mainly to animals, the observation that the immune system realizes various activities beyond defense holds across all living organisms; for example, CRISPR-Cas systems in prokaryotes participate not only in defense but also in repair.

Many of the same actors that ensure the defense of the organism against pathogens, therefore, are equally central for processes previously considered as nonimmune and which overlap to a significant degree (Figure 2.2). Perhaps one could even consider that the very division of these processes into such categories as "defense," "repair," and "development" reflects more the way we, as investigators, address questions about bodily systems (and divide such processes into convenient categories) than real differences in nature. From this point of view, there would be much to say in favor of a revised epistemology of immunology, understood as a reflection on how the categories by which the immune system has been conceived (in the context of the division into systems) could be redefined and redrawn.

2.4 Accounting for the Evolution of Immunological Processes and Attributing a Function to the Immune System Have Become Difficult

The extension of immunity well beyond defense has consequences for two central issues, namely the evolutionary history of immune systems and