Journal of the History of Biology (2014) 47:411–442
DOI 10.1007/s10739-013-9370-z

Immune Balance: The Development of the Idea and Its Applications

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Abstract. It has long been taken for granted that the immune system's capacity to protect an individual from infection and disease depends on the power of the system to distinguish between self and nonself. However, accumulating data have undermined this fundamental concept. Evidence against the self/nonself discrimination model left researchers in need of a new overarching framework able to capture the immune system's reactivity. Here, I highlight that along with the self/nonself model, another powerful representation of the immune system's reactivity has been developed in the twentieth century immunology. According to this alternative view, the immune system is not a killer of nonself strangers but a peace-maker helping to establish harmony with the environment. The balance view of the system has never become part of the dominant paradigm. However, it is gaining more and more currency as new research develops. Advances in mucosal immunology confirm that instead of distinguishing between self and foreign the immune system reacts to microbial, chemical and self-induced alterations to produce responses that counterbalance effects of these changes.

Keywords: Burnet, Immune balance, Immune equilibrium, Immune self, Metchnikoff, Self/nonself recognition

Introduction

One of the central problems of immunology is that of how the immune system manages to protect an individual from disease-causing agents while tolerating harmless antigens and healthy tissues. Failure to produce accurate responses can lead to autoimmune diseases, allergy, cancer, infection or tissue damage. Therefore, understanding the basic

principle that allows the immune system to orient itself in a variety of chemical, microbial and self-derived stimuli is of crucial importance.

Throughout the second half of the twentieth century it was taken for granted that the immune system manages to benefit the organism thanks to its power to tell self from nonself (Tauber 1994, 2009). It seemed intuitively plausible to assume that the immune system like any other protective system must be able to recognize and react to strangers in order to play its defensive function. Thus the self/nonself model has become an important conceptual framework, a vantage point from which phenomena like autoimmunity, organ graft rejection and infectious diseases were understood. Indeed, the self/nonself model helped to establish a paradigm, the ''governing principle of immunology'' (Silverstein and Rose 1997). Immunology has become ''the science of self/nonself discrimination'' or ''the science of self'' (Klein 1984; Lopez-Larrea 2012; Wilson 1971).

Recent experimental studies have challenged this paradigm. They have provided evidence showing that the immune system does not discriminate between self and foreign. Quite the contrary, immune reactions to self-tissues and tolerance to foreign bodies turned out to be crucial for ensuring health and well-being (Pradeu 2012, pp. 85–130). Several unsuccessful attempts have been made to fix the paradigm in crisis and now there is need for a new conceptual framework able to make sense of the immunological data. Here we reveal that one powerful idea able to address the shortcomings of the classical model has already been present in immunology from its inception. If brought into light and modified according to the current evidence this idea may inform a new paradigm of the immune system function.

The Paradigm of Self/Nonself Discrimination and Its Decline

According to Alfred Tauber, the seed of the idea of immune self was planted by Elie Metchnikoff (Tauber 1994). Indeed, as we shall see, Metchnikoff was first to suggest that the immune system (phagocytes) determines the confines of the organism thereby defining the limits of self (Tauber 1994, 2003; Pradeu 2012).

Elie Metchnikoff was a comparative embryologist whose studies of the development of germ layers in invertebrate embryos brought him to analyze function of a class of mesodermal amoeboid cells he called ''phagocytes'' (Chernyak and Tauber 1990; Tauber 2000). He suggested that phagocytes evolved from unicellular organisms that use their

phagocytic function for intracellular digestion of nutrients (Metchnikoff 1905, p. 520). In multicellular organisms, already equipped with complex digestive systems, these cells were assumed to be involved in ensuring immunity and adaptation (Metchnikoff 1905, pp. 520–522).

To explain the role of phagocytes in immunity of vertebrates, Metchnikoff applied a method of comparative pathology which involved studies of analogous pathological processes in living beings from unicellular organisms to higher mammals (Metchnikoff 1893, p. 12, 27). He believed that organisms as simple as amoeba can be subject of infection and disease and that immunity in these organisms is mediated by their digestive systems and repulsion mechanisms. The digestive systems of Protozoa were assumed to be able to eliminate any type of digestible organic material that cannot resist their destructive action. Thus, to avoid being eliminated an organic material had to defend itself from the activity of digestive secretions of the Protozoon like amoebodiastase, trypsin or pepsin (Metchnikoff 1893, pp. 18–28). Accordingly, Metchnikoff argued that the reason why a unicellular organism does not digest its own organelles is because these organelles ''possess a power of defending themselves against the attack of the digestive secretions'' (Metchnikoff 1905, p. 16).

The idea that immunity is a matter of struggle between digestive power of one agent and susceptibility of another has been extended to higher mammals (Metchnikoff 1905, p. 545). Metchnikoff believed that specialized digestive cells, phagocytes, can eliminate ''all sorts of solid matter'' that cannot resist their phagocytic power regardless of the origin of this matter and its identity. Consequently, he assumed that phagocytes may not only remove foreign invaders but also destroy cells of the body that are not able to protect themselves from phagocytosis. By analogy to amoeba that avoids being self-digested thanks to resistance of its own organelles, Metchnikoff proposed that in order to survive, cells of the body have to constantly defend themselves from being phagocytosed (Metchnikoff 1892(2000), p. 214).

Metchnikoff maintained that the tension between resistance of bodily cells and devouring power of phagocytes (mostly macrophages) creates a conflict: ''The word conflict is not used metaphorically in this case. It is a veritable battle that rages in the innermost recesses of our beings'' (Metchnikoff 1903, p. 239). If cells of the body fail to protect themselves from being phagocytosed, senile atrophy can occur. In this condition, weakened cells of the organism become engulfed and replaced by ''elements of lower kind'' like connective tissues (Metchnikoff 1903, pp. 235–236). This destruction and replacement was assumed to lead to

hypertrophy and hardening of organs giving the observable symptoms of dementia and general physical decline. Thus, as a method of life extension, Metchnikoff considered removal of phagocytes by antibodies or strengthening ''higher elements of the body'' in their fight with phagocytes (Metchnikoff 1903, pp. 228–258; Ehrlich 1900, p. 448).

As one can see, Metchnikoff believed that phagocytes are not aimed at pathogens or foreign tissues specifically. By eliminating susceptible organic materials regardless of their origin, these cells were able to define morphology of the organism, the course of its development and the forms of its interaction with the environment (Metchnikoff and Elie 1892; Tauber 2003, pp. 899–900). Indeed, Metchnikoff believed that the function of phagocytes in maintaining integrity of the organism was subordinated to their primary role in determining the identity of that organism (Tauber 1994, p. 20). ''Metchnikoff's phagocytosis theory was less an explanation of host defence than a proposal that might account for establishing and maintaining organismal 'harmony''' (Tauber 2003, p. 897). Because of their identity-determining function, phagocytes were assumed by Metchnikoff to have the highest degree of autonomy among cells of the body (Metchnikoff 1905; p. 566). Indeed, despite believing that phagocytes can engulf any type of susceptible matter, Metchnikoff assumed that these cells are equipped with a certain degree of selectivity in the form of positive and negative chemotaxis. He suggested that changes in the concentration of chemicals could direct their migration to microbes, foreign animal cells, or weakened self-tissues (Metchnikoff 1892(2000), p. 214; Metchnikoff 1905, p. 548). Nevertheless, specificity of phagocytes was highly limited as the scope of their potential targets was extremely broad (Silverstein 2009, p. 139). All in all, instead of assuming that the properties of being self and foreign are fixed at some point in ontogeny to become recognized as such in the adult, Metchnikoff believed that phagocytes *constantly* define what self and nonself is. Thus, Metchnikoff played a crucial role in formulating the idea of immune self: ''For him, the embryologist, the individual was not given, but underwent constant change as it developed and adapted to ever-changing inner and outer environments'' (Tauber 2003, p. 901).

Several decades after Metchnikoff, the Australian immunologist Macfarlane Burnet reflected on the very same problem that perplexed the Russian researcher. He asked how a Protozoon like amoeba manages to absorb organic matter without digesting its own organelles (Burnet 1940, p. 29). His answer was very different from that of Metchnikoff. He did not suggest that amoeba avoids self-digestion because its organelles defend themselves from the action of digestive

secretions. Instead, he proposed that amoeba avoids self-digestion because it has power to recognize nutrients as foreign and to distinguish them from self. He extrapolated the conclusion to the immune system and proposed that the fundamental capacity to recognize foreignness allows higher organisms to defend themselves from infection and disease while making it possible for animals to tolerate their own tissues (Burnet and Fenner 1948).

Why Burnet needed to postulate special mechanism of self/nonself discrimination instead of assuming simply, like Metchnikoff, that it is *susceptibility* to being destroyed that decides about the fate of organic matter? To answer this question we have to realize that despite sharing an antireductionist biological stance with Metchnikoff (Tauber 1994, p. 88), Burnet was a follower of the humoralist tradition in immunology. Not only did he apply serological methods in his experimental work but also believed that immune responses are mediated by antibodies (Fenner 1987, p. 44; Mackay 1991, p. 301). Early proponents of the humoralist tradition like Hans Buchner and Paul Ehrlich assumed that antibodies or complement molecules target *foreign* agents specifically and that self-responses are expressions of pathological conditions within the host (Ehrlich 1910, p. 364). For example, Paul Ehrlich insisted that there must be special ''regulatory contrivances,'' which prevent immune molecules from attacking self-tissues and which ensure that immune responses are aimed at foreign agents (Ehrlich and Morgenroth 1910, p. 25). To understand how these mechanisms operate, Ehrlich investigated the phenomenon of hemolysis in which injection of *foreign* blood leads to the production of a toxin called hemolysin (Ehrlich and Morgenroth 1910). Together with Morgenroth, he observed in goats that hemolysin produced in the presence of injected foreign blood never destroys the blood of the recipient but is specific to many other types of foreign blood (Ehrlich and Morgenroth 1910, pp. 27, 30). To account for this observation the authors proposed that blood cells of the recipient lack receptors that could bind hemolysin (Ehrlich and Morgenroth 1910, pp. 28–29). Even though Ehrlich and Morgenroth assumed that in most cases hemolysin cannot act as an *autolysin* (autotoxin), they considered this possibility in rare cases of injection of foreign blood. Nevertheless, they insisted that even if *autolysin* was generated in such cases, its presence would automatically induce the production of *antiautolysin* that would neutralize the toxin and prevent it from destroying blood of the recipient (Ehrlich and Morgenroth 1910, pp. 32–33). These ideas supported the doctrine of ''horror autotoxicus,'' according to which production of autoantibodies

would be "dysteleological to the highest degree" (Ehrlich 1910, p. 388; Silverstein 2002, p. 112).

Thus, as one can see, the idea of self/foreign discrimination was present in the humoralist tradition well before Burnet. The Australian researcher contributed to the debate by suggesting that self/foreign recognition is not genetically encoded but can be learned during development (Burnet and Fenner 1949, pp. 85–86; Tauber 1994, p. 99; Silverstein 2009 p. 165). He arrived to this conclusion based on his studies of Owen (1945), Loeb (1937), Huxley (1926) and Whitehead (cf. Warwick and MacKay 2013). To account for this phenomenon of learning Burnet formulated two distinct hypotheses (Baxter 2006; Mackay 1991).

The first was "self-marker hypothesis." During his studies of the antibody responses to exotoxins of *Staphylococcus aureus* in rabbits, Burnet found that there is a stepwise increase in the antibody concentration following primary and booster immunization. This augmentation in antibody production could not be explained by instructivist theories, which presupposed that antibodies were produced only in the course of direct interaction with the antigens (Fenner 1987, p. 46; Silverstein 2009, pp. 43–67). Thus, Burnet speculated that some cellular mechanism that preserves information about an antigen must be involved in antibody production. He proposed that antibody-producing cells bear special adaptive enzymes that adapt during embryogenesis to "fit" into self-markers (i.e. molecular patterns characteristic of the individual) (Silverstein 2009, pp. 54–56). If confronted with nonself-antigens later in life, these enzymes were assumed to undergo structural modifications to impress information about the antigen on the genome, thereby becoming indirect templates for subsequent antibody production (cf. Burnet and Fenner 1948, pp. 314–317; 1949, pp. 102–103).

Burnet did not feel comfortable with the Lamarckian flavor of the idea that antigens can modify enzymes and imprint inheritable information upon the antibody-producing cells. Therefore, he abandoned the "self-marker hypothesis" to formulate a new theory of self/nonself discrimination. In 1957, inspired by the Jerne's Natural Selection Theory and Ehrlich's Side Chain Theory, Burnet established Clonal Selection Theory (CST) that helped to understand the process of antibody responses in mammals (Warwick and MacKay 2013). Jerne proposed that there is a large repertoire of antibodies (globulin molecules) of random specificities that can recognize any foreign antigen. When an antigen binds to a complementary antibody, it creates a complex which can become phagocytosed by an antibody-producing cell to stimulate

production of replicas of the engulfed antibody (Jerne 1955). Seizing upon the comment of Talmage that the theory by Jerne would be more plausible if antigen receptors were conceived as bound to lymphocytes, Burnet proposed that antigens select clones of lymphocyte antigen receptors rather than free antibodies in the blood plasma (Burnet 1957, p. 68). To explain the capacity of the immune system to react to foreign antigens, Burnet suggested that those lymphocytes whose receptors recognize self-antigens become deleted in an embryo leaving a repertoire of clones that can recognize any foreign antigen in the adult: "Self not-self recognition means simply that all those clones which would recognize (that is, produce antibody against) a self-component have been eliminated in embryonic life. All the rest are retained" (Burnet 1959). Thus, according to the Burnet's terminology, the immune system recognizes self in the embryo and nonself in the adult.

By suggesting that adults are left with a repertoire of clones that recognize only foreign antigens, Burnet assumed that no antigen receptors of new specificities can be generated later in life. However, accumulating data revealed that new lymphocytes are produced also in the adults. Joshua Lederberg modified CST to accommodate this fact. He proposed that instead of being eliminated only in an *embryo*, self-reacting clones are also deleted at the early stages of *lymphocytes'* development (Lederberg 1959). Thus Lederberg assumed that lymphocytes have different sensitivities before and after maturation. Their stimulation at the initial stages of their development leads to their removal while their activation after maturation provides a survival signal and induces their proliferation (Lederberg 1959, p. 1651). Burnet accepted this modification of CST because it provided a more realistic mechanism of clonal deletion than the original version of his theory (Burnet 1964). Further research supported the modified version of CST by showing that B-cells can be tolerized if exposed to an antigen at the early stages of these cells' development and that auto-reactive T-cells are eliminated in the thymus (Gurr and Viret 2009; Kappler et al. 1987).

Despite its initial success, the paradigm of self/nonself discrimination has been facing increasing conceptual and experimental problems. Firstly, accumulated data on the acquisition of tolerance have revealed that many of the self-reacting clones are not deleted in an embryo and that tolerance can be induced also in the adult (Silverstein and Rose 1997, pp. 199–200). Secondly, it has been shown that autoimmunity is an essential part of the organism's physiology helping to regulate immune responses and maintain self-tissues (Cohen 1992; Coutinho et al. 1995; Quintana and Cohen 2004). Thirdly, despite the mechanism of

allogeneic graft rejection was elucidated, recognition of bacterial nonself was left unexplained (Pradeu 2012). Fourthly, it became clear that many invertebrates do not exhibit histoincompatibility, thereby indicating that self/nonself discrimination is not the essential feature of the immune system (Klein 1999). Fifthly, it became clear that the activity of antigen presenting cells (APCs) that initiate and control adaptive responses, depends on innate immune receptors recognizing motifs shared by self and nonself agents (Winchester et al. 1984; Erridge 2010). Sixthly, the paradigm of self/nonself discrimination was not able to account for tolerance to dietary materials or to commensal bacteria in the gut. Finally, the classical paradigm was questioned on the grounds that the very concept of immune self is nebulous and calls for precise explication in molecular terms (Tauber 1994).

In the face of the criticism of the self/nonself discrimination model (see Pradeu 2012; Tauber 2009 for more detailed reviews), researchers attempted to fix the paradigm in crisis. To take into account that the immune system ignores innocuous nonself antigens, Janaway and Metzhitov proposed that the immune system distinguishes between infectious nonself and noninfectious self rather than between self and nonself (Janeway 1992). Furthermore, it was suggested that markers that can activate adaptive responses include microbial patterns and abnormal self-markers and that these markers and patterns are recognized by dedicated receptors (Medzhitov and Janeway 2002). However, it became clear that most pattern recognition receptors (PRR) do not respond to microbial nonself motifs exclusively. Instead, PRRs believed as sensitive to bacterial products exclusively were demonstrated to react also to self-patterns. In addition, tumor antigens have turned out to be mostly normal self-antigens (Cohen 2000a; Pardoll 1999). Finally, the modified self/nonself model, like its original version, was not able to account for physiological autoimmunity and sterile inflammation.

More radical revision of the classical model came from Polly Matzinger who argued that the immune system evolved mechanisms to recognize danger rather than self and nonself. This danger recognition was assumed to be mediated by immune receptors that react to exogenous microbe-associated molecular patterns (MAMPs) and to endogenous molecules released during stress or tissue damage (Matzinger 1994; 2002). However, most recent evidence undermines this model demonstrating that innate immune receptor ligands cannot serve as markers of danger as their activation can play not only immunostimulatory but also immunosuppressive functions (Kubinak and Round 2012). Moreover, the same type of an innate immune receptor ligand can act as a

danger signal or a safety signal depending on the context of other receptors stimulation (Foster et al. 2007). Finally, there has been an argument that the notion of danger is not well defined and depends on a posteriori interpretation: "the immune response is induced by a danger signal, but the danger signal is defined as just about anything that can induce an immune response" (Medzhitov and Janeway 2002, p. 300; Pradeu and Cooper 2012). Thus, neither the paradigmatic self/nonself model nor its recent permutations managed to provide an accurate overarching account of the immune system activity. This left researchers in need of a new paradigm in immunology.

The Idea of Immune Balance

Along with the self/nonself discrimination model, another powerful account of the immune system function has been developed in immunology. According to this alternative view, the primary role of the system is not to recognize and fight nonself strangers but to harmonize interactions between the individual and its environment. Here we focus on the development of this view to see how it fits into the current experimental data in mucosal immunology.

As we have seen, Metchnikoff extended the Darwinian notion of struggle for existence to describe interactions between cells (Silverstein 2009, pp. 432–434; Tauber 1994, p. 21). Importantly, he also went one step further than Darwin in his understanding of adaptation. Darwin focused on adaptation at the species level, because, for him, evolution was not driven by adaptive transformations of individuals but by selection of those variants of species that are more successful than others in their struggle for existence (Darwin 1859; Lewontin 1983). Instead, Metchnikoff considered adaptation at two levels: at the species level and individual level.

He referred to the process of adaption at the species level as *harmonization* (Metchnikoff 1903, pp. vi; 19–32). Accordingly, the lack of adaptation of species to their environment was synonymous with *disharmony* (Metchnikoff 1903, p. 87). For Metchnikoff, the archetype of perfect harmony was the mechanism for the fertilization of orchids (Metchnikoff 1903, p. 39). In contrast to orchids, humans were believed by Metchnikoff to be essentially disharmonious creatures that are morphologically and physiologically ill-adapted to their environment (Tauber and Chernyak 1991). As an example of disharmony of the human species, he analyzed maladaptation of the digestive system to

changes brought about by modern civilization. He believed that morphology of the intestine was shaped by particular needs of our ancestors and that in its present form it reduces the life span of people by hosting excessive amounts of microbes that poison the body (Metchnikoff 1903, pp. 248–257).

Metchnikoff assumed that the chief harmonizing factor at the species level is Darwinian natural selection: ''Harmonious characters are more abundant in nature than injurious peculiarities … The useful qualities are handed down and preserved, while noxious characters perish and so disappear'' (Metchnikoff 1903, p. 38). He argued that humans can follow harmony at the species level by adopting ''orthobiosis,'' that is a scientifically grounded conduct of behavior that ensures the optimal conditions for the maintenance of health and prolongation of life (Metchnikoff 1908, pp. 327–328). As Olga Metchnikoff put it, Elie Metchnikoff believed that: ''science, by revealing the laws of Nature, applied to humanity the benefits derived from them, whilst striving to counterbalance their cruel or harmful effects'' (Metchnikoff 1924, p. 164).

Apart from considering adaption of species, Metchnikoff also analyzed adaptation of individuals to their local environment. He assumed that this type of adaptation could be achieved in the course of struggle for existence between phagocytes and other cells. Consequently, mutual adaption in the form of symbiosis or commensalism was not considered to be an outcome of cooperation but a product of an equilibrated struggle between parasites and phagocytes (Metchnikoff 1884, 1905, p. 17; Tauber and Chernyak 1991, p. 141). In addition, Metchnikoff believed that phagocytes promote adaptation of the individual by directing development of the organism. Indeed, he assumed that phagocytosis of bodily cells does not always lead to atrophy. He argued that there is a variety of specific phagocytes that reside in the nerves, muscles and bones, which are ready to eliminate weaker cells in these tissues to leave room for their replacement by stronger cells. As a result of this replacement, those body parts that are needed for adaptive adjustments become reinforced and enlarged (Metchnikoff and Elie 1892(2000), pp. 210–214; Metchnikoff 1908, pp. 18–24). Moreover, Metchnikoff assumed that phagocytes play an important role in the early stages of development by ensuring harmonious growth of the organism. As an example of this function, he considered the activity of phagocytes in the metamorphosis of amphibians (Metchnikoff 1893, pp. 94–110; Tauber and Chernyak 1991, p. 132).

Metchnikoff was not the only researcher who at the beginning of the twentieth century tried to rephrase categories like adaptation and symbiosis in terms of struggle for existence. Since the work of Pastorians in the 1880s it was generally accepted that the outcome of parasite/host interactions depends on the balance between antagonistic forces of virulence and resistance (Mendelsohn 1998, p. 319). Most notably, this idea was embraced by the American microbiologist, Theobald Smith who is famous for the discovery of the etiology and the means of transmission of Texas cattle fever (Dolman and Wolf 2003, pp. 80, 99–121; Méthot 2012; Schultz 2008). The studies of the cattle fever gave Smith an opportunity to observe that severity of a disease may depend on the duration and stability of the interaction between a parasite and its host. Indeed, he found that the disease is asymptomatic in the cattle originating from the territory where the infectious agent is present permanently, while it is severe in animals coming from other areas. This observation suggested that the infectious agents causing the disease enter into a symbiotic carrier state in the animals that manage to establish harmonious relationships with the agents.

The study of the asymptomatic carrier state of the protozoon causing Texas cattle fever inspired Smith to draw general conclusions concerning the ecology of parasite/host interactions (Dolman 1984, p. 578; Méthot 2012, p. 272). He argued that there is no advantage for a parasite from killing or damaging the host. Quite the contrary, high degree of virulence may interfere with the capacity of the microbe to escape to another host: ''The tendency of all invading microorganisms in their evolution toward a more highly parasitic state is to act solely on the defensive while securing opportunity for multiplication and escape to another host'' (Smith 1904, p. 821). Thus, he maintained that in the course of evolution of a parasite/host interaction there is a gradual decrease in the pathogenicity of microbes and development of power to equilibrate defenses. Accordingly, an unequilibrated struggle between a parasite and the host that manifests itself in a disease is indicative of a phylogenetically recent association between the organisms (Smith 1904, 1921, p. 102).

The idea of equilibrium elaborated by Smith was further developed and popularized by the American bacteriologist Hans Zinsser who was a friend and devoted adherent of Smith. Zinsser is famous for his popular books and textbooks on bacteriology as well as for his research on typhus vaccine (Summers 1999b). In the book *Infection and Resistance* he addressed the same problem that puzzled Metchnikoff. To elucidate the problem of tolerance and immunity he asked the question

of why an organism does not digest its own tissues (Zinsser 1914, p. 6). His answer was very similar to that of Metchnikoff, as he suggested that the tissues of the body avoid self-digestion because they resist the action of gastric juices. He argued that analogous counterposition of defensive and offensive forces lies at the heart of mutual adaptation of parasites and their hosts. Thus, Zinsser followed the tradition of thinking about parasite/host interaction in terms of balance or equilibrium (Zinsser 1914).

The balance view of the parasite/host relationship and "the law of declining virulence" were developed in a unique context by the Canadian biologist Felix d'Herelle. D'Herelle discovered a lytic agent able to provoke death of the dysentery bacteria in human patients (d'Herelle 1917; Summers 1999a, pp. 47–59). He referred to this agent as bacteriophage (or phage) and identified it as an obligatory parasite of bacteria (d'Herelle 1922). He proposed that bacteriophages are continuously present in the gut where they play an important role in the immunity of their hosts (d'Herelle 1922, pp. 170–171). This continuous presence of phages in the gut (or in a culture) was assumed to depend on the state of equilibrium between virulence of phages and resistance of bacteria that was induced by antagonistic modulation between these forces (d'Herelle 1922, p. 80; 1926, p. 211; Sapp 1994, pp. 107–108). Perturbation of the balance between virulence and resistance could give an advantage to either bacteria or bacteriophages affecting the course of a disease in the host (d'Herelle 1922, pp. 76–80, 274; Summers 1999a, p. 59). d'Herelle referred to this imbalance to explain the phenomenon of "lysogeny," that is spontaneous lysis of bacteria after a period of apparent absence of a virus (d'Herelle 1926, pp. 210–212, 230–231; Sankaran 2008).

d'Herelle pointed out that bacteria cultured with bacteriophages can be eliminated or not depending on their susceptibility to the bacteriophages' action. Those that are resistant survive and proliferate while vulnerable ones perish. In the meantime, phages undergo analogous selective process. They survive and proliferate only if are virulent enough to parasitize bacteria. As a result, there is "a continual selection with the indefinite co-existence of the two antagonists. Such mixed cultures, symbiotic in nature, can be subcultured indefinitely" (d'Herelle 1926, p. 211). These considerations led d'Herelle to believe that the interaction between the parasite (phage) and its host (the bacterium) gradually moves towards perfect equilibrium:

> One finds by experiment that the stability of mixed cultures is the greater as the symbiosis is of longer duration … If one finds that

> after a dozen subcultures … the symbiosis continues, it is rare that it can not be maintained indefinitely …It is not solely a test tube experimental phenomena but one which occurs also in nature (d'Herelle 1926, p. 212).

Overall, for d'Herelle, both bacteriophages and bacteria had remarkable power to adapt to each other's increase in virulence and resistance (d'Herelle 1922, p. 274).

As one can see, d'Herelle's ecological views came close to those of Smith and Zinsser. They shared similar understanding of a carrier state of a parasite and the idea that virulence of successive generations of a microbe declines over time. Nevertheless, it is impossible to find any references to Smith and Zinsser in the work of d'Herelle. William Summers (personal communication) points out that d'Herelle and Zinsser worked at the Pasteur Institute during World War I and that it is not impossible that these two authors met. d'Herelle himself admitted that his views on the relationship between bacteriophages and bacteria were inspired by the ideas of the French botanist, Noël Bernard who is famous for his study of the symbiosis between fungi and seeds of orchids (d'Herelle 1926, p. 211, 423; 1922, p. 80). According to Bernard, mutually beneficial relationship between the two species is a result of a balance between offensive forces of the fungus and defensive powers of the orchid (Bernard 1902; Sapp 1994, p. 79). The French Botanist understood symbiosis as "the association of two specifically distinct beings which harmonize their functions for the greater good of the community" (Bernard 1902, p. 5; Transl. Sapp 1994, p. 78). d'Herelle applied Bernard's interpretation of symbiosis to his studies of bacteriophages and defined it as a "parasitism *balanced* by the resistance to infection" (d'Herelle 1926, p. 211).

The idea that parasite/host interactions can be framed in terms of balance as well as the concept of decreasing virulence lied at the heart of experimental and theoretical work of Macfarlane Burnet. Even though Burnet denied that his ecological views were inspired by those of Theobald Smith (Burnet 1968, p. 23), he knew Smith's ideas from the book *Rats, lice and history* by Zinsser (Burnet 1942, p. 131; Zinsser 1934, p. 46). In addition, Burnet's early research was focused on bacteriophages and the phenomenon of lysogeny which gave him an opportunity to become familiar with ecological ideas of d'Herelle (Tauber 1994, pp. 88–91; Sankaran 2010). Engraved in Burnet's memory was his first reading of the d'Herelle's book *The bacteriophage; its role in immunity* (Sexton 1991, p. 43).

At the beginning of his phage research, Burnet believed that only few cases of lysogeny could be explained, like in d'Herelle, in terms of

unbalanced struggle between bacteria and bacteriophages (Burnet and McKie 1929, p. 282). However, later he admitted that given a particulate nature of phages ''one is almost forced to postulate that each bacterium carries in intimate symbiosis one or more phage particles'' (Burnet 1934, p. 346, cf. Park 2006, pp. 501–502). Like d'Herelle, he considered symbiosis to be a state of stable equilibrium between naturally occurring populations of bacteria and phages. Indeed, he pointed out that the massive phage-induced lysis observed in the lab cannot take place in nature, because it would lead to eradication of all phage-sensitive bacteria. Instead, ''a form of a dynamic equilibrium must be set up by which a fairly constant proportion of both species manage to survive'' (Burnet 1934, p. 345). Thus he rejected the hypothesis that bacteriophage could be a unit of a bacterial chromatin (Burnet 1934, p. 346).

Burnet found similarity between the apparent latency of the phage in lysogeny and the ''carrier'' nonpathogenic state of infectious microbes that reside in the tissues of healthy people: ''my stock [of phage/bacteria] culture which is in every respect an apparently healthy and thriving lot of individuals has a disease in a latent form like a man with diphtheria bacili in his throat that don't quite give him dip'' (Burnet 1926; quote after Sankaran 2010, p. 373). He believed that this mutual tolerance between the parasite and the host is an effect of a balanced coexistence of the bacteria with their human hosts over many generations. Thus Burnet's idea that parasite/host interactions gravitate towards the state of equilibrium and symbiosis has been extended to apply to all types of predator–prey relationships (Burnet 1934, pp. 345–348, 1940, pp. 5–11; Park 2006, p. 512).

The same ecological framework was used by Burnet in the 1930 s to explain the etiology of Q fever, a disease of abattoir workers in Brisbane. He discovered the causative agent of the disease (*Coxiella burnetii*) and argued that it was a type of rickettsia (Burnet and Freeman 1937). He pointed out that rickettsiae are innocuous symbionts or semiparasites of insects and that their colonization of human hosts should be considered as an incident. As new and accidental hosts, humans were not able to maintain stable equilibrium with these parasites and therefore suffered from severe symptoms of Q fever (Burnet 1942). By so explaining the epidemiology of Q fever, Burnet repeated the idea formulated by Hans Zinsser that rickettsial diseases follow the pattern of pathologies that result from an unbalanced struggle between a parasite and the host (Burnet 1940, p. 72, 1942, p. 131; Zinsser 1934). Indeed, as we have mentioned, Burnet was familiar the book *Rats, lice and history*,

where the American bacteriologist was quite explicit about the details and the origin of the balance view of the parasite/host interaction: ''As Theobald Smith states it, pathological manifestations are only incidents in a developing parasitism. On this basis Rickettsia infection in the ticks is a very ancient condition; for in this relationship mutual tolerance has developed to such perfection that neither partner appears to be injured'' (Zinsser 1934, pp. 225–226).

Burnet used the same general framework to explain etiology of other infectious diseases in humans. For example, he argued that psittacosis, known to be a serious disease of humans, was a latent, asymptomatic disease of wild parrots (Burnet 1936). Again, according to Burnet, the difference in the susceptibility to the disease between parrots and humans reflected the level of stability that these organisms managed to establish with their parasites (Burnet 1936, p. 102). All things considered, following d'Herelle and Zinsser, Burnet assumed that an infectious disease should be understood as ''a conflict between man and his parasites which, in constant environment, would tend to result in a virtual equilibrium, a climax state, in which both species would survive indefinitely'' (Burnet 1940, pp. 23–24).

How did Burnet conceive the mechanism that allows establishing the equilibrium? He assumed simply like d'Herelle that there is a negative feedback that automatically controls the number of parasites and their hosts (Burnet 1940, p. 8). He argued that an increase in the number of predators leads to a decrease in the number of prey. This in turn, reduces the number of predators thereby leading to a subsequent increase in the number of prey and so the circle continues (Burnet 1940, p. 8). Burnet illustrated this oscillatory dynamics in the form of waves of prevalence of endemic diseases that fluctuate from the state of epidemics to the state of latency over generations (Burnet 1940, p. 188). Interestingly, he also argued that the process of establishing host/parasite equilibrium is also associated with a decrease in the opposing pressures of virulence and resistance: ''Nature prefers that neither host nor parasite should be too hard on the other'' (Burnet and White 1972, p. 82). Joshua Lederberg said that ''since Frank Macfarlane Burnet, Theobald Smith, and others, we have understood that evolutionary equilibrium favors mutualistic rather than parasitic or unilaterally destructive interactions'' (Lederberg 1993).

To complete our survey of the development of the idea of balance in immunology we should note that this idea was used in a different sense to describe interactions between cellular and molecular components of the immune system. The balance way of thinking about bodily parts can

be traced back to ancient Greece (Arikha 2007). Like the concept of self/foreign discrimination, it was introduced to immunology by early humoralists at the beginning of the twentieth century. The American-British serologist, George Nuttall, pointed out that Ehrlich's side chain theory was based on the concept that an organism maintains equilibrium between its parts and that this equilibrium is induced by "mutually restraining influences exerted upon each other by the cells which compose it" (Nuttall 1904, p. 6). The idea of equilibrium between bodily parts was originally formulated by Ehrlich's cousin, Carl Weigert, who believed that a damage inflicted to a bodily part can perturb the intrinsic balance of the organism and initiate a reparative reaction in the form of compensatory hyperplasia whose function was to restore the equilibrium (Nuttall 1904, pp. 6–7; Ehrlich 1908, p. 307). Following this idea, Paul Ehrlich argued that binding of foreign elements to cell receptors excludes these receptors (or side chains) from reacting to other stimuli and therefore demands compensation in the form of newly synthesized unbound receptors. He believed that this reparative process could take the form of *overcompensation* that is excessive production of receptors that might no longer manage to attach to the cell surface but become released into the blood plasma as free anti-toxins (Ehrlich 1900, pp. 436–437). This release of antibodies was believed by Ehrlich to be able to neutralize the activity of the toxin and to restore the balance within the body (Nuttall 1904, p. 10; Silverstein 2002, pp. 77–91).

The idea that the immune system maintains equilibrium between its parts was also hinted several decades later by Burnet. This concept was not directly influenced by Ehrlich and other early proponents of the idea. Rather, it was derived from Burnet's ecological thinking. Indeed, the Australian immunologist maintained his dynamic ecological outlook throughout his entire career. This view preceded his self/nonself discrimination model and organized his thinking about interactions between immune and nonimmune cells. He insisted that central tenets of CST can be derived from basic principles that govern natural and artificial selection of clones in populations of bacteria or viruses (Burnet 1959, pp. 9–29). He pointed out that random mutations accumulate with each successive generation of bacterial clones and that some of these clones thus get an advantage to expand in the population. This idea was related to his previous findings indicating that repeated multiple passages of influenza viruses can alter their pathogenicity (Burnet 1937). Moreover, the dynamic ecological perspective led Burnet to emphasize that one of the most fundamental properties of large populations of cells (microbes or somatic cells in the body) is their tendency

to establish ecological equilibrium (Burnet 1959, p. 12). This idea was later used by Burnet to explain pathogenesis of autoimmune diseases and other immunopathological conditions.

To account for the factors that ensure equilibrium between bodily parts, Burnet postulated special homeostatic mechanisms that regulate interactions between immune and nonimmune cells. By controlling number and composition of cells in the body these mechanisms were assumed to play a variety of functions such as modulation of the concentration of immunoglobulins in the blood (Burnet 1969, pp. 92–93), prevention of cancerogenesis (Burnet 1959, p. 193) and neutralization of self-reacting antibodies (Burnet 1959, p. 134). In fact, while formulating CST, Burnet was already aware that postulated somatic mutations generating diversity of lymphocyte antigen receptors may produce autoreactive clones that recognize self-antigens (Burnet 1959, p. 122). He believed that persistence of such ''forbidden'' clones could perturb homeostasis within the body and trigger an autoimmune disease (Burnet 1969, pp. 255–285). He speculated on the nature of the homeostatic mechanisms that prevent such self-reactive clones from inducing immune pathology. One possibility was that the disease-causing potential of auto-antibodies is minimized by release of some regulatory antibodies competing with the forbidden clones in binding to self-antigens (Burnet 1959, p. 145). Another possibility was that self-reacting clones are readily recognized and eliminated (Burnet 1959, p. 128; Mackay and Burnet 1963). It was this latter option that was later confirmed experimentally (Mackay 2008).

The notion that the immune system is concerned with maintaining homeostatic balance between its parts was elaborated more extensively by Niels Jerne whose ideas were deeply inspired by those of Paul Ehrlich (Silverstein 2009, pp. 211–230). In 1973 Jerne formulated ''immune network theory'' that was based on the assumption that each antibody molecule can act as an antigen for another antibody (Jerne 1974). According to Jerne's terminology, the binding site of an antibody, paratope, may not only bind to a fragment of a surface of a foreign antigen (epitope) but also to a part of a molecular surface of a variable region of another antibody called idiotope. Thus, he assumed that antibodies can create a dynamic self-regulatory network of interconnected elements (Eichmann 2008, pp. 82–94; Söderqvist 2003). In the steady-state conditions this network was believed to maintain equilibrium established by suppressive forces of antibodies that bind to paratopes of other antibodies and stimulatory effects of those antibodies that bind to idiotopes and epitopes. This dynamic balance between idiotypes

and anti-idiotypes could be perturbed by the presence of an external antigen. Thus it was assumed by Jerne that the fundamental role of the immune system is to reestablish perturbed equilibrium by producing an appropriate antibody reaction (Jerne 1985).

Towards a New Paradigm in Immunology

As one can see, apart from the view of the immune system as a sensor and killer of foreign agents, there has also been a concept that the system helps to establish harmonious balance with the environment. At the face value, these two views are diametrically opposed. However, a closer scrutiny reveals that depending on the interpretation they may be reconciled. Indeed, as discussed above, many advocates of the self/nonself model appeared to be also proponents of the idea of immune balance.

There has been at least three different ways in which the idea of immune balance was understood. Researchers like Burnet and d'Herelle focused on the balance in *the ecology of parasite/host populations*. These authors did not understand equilibrium as a relationship between a single organism and its parasite (like between a single bacterium and a phage or a single patient and his colonizing *Rickettsia)*. Instead, as we have seen, they defined immune equilibrium as a stable ratio between parasites and their hosts induced by opposing pressures of virulence and resistance. Burnet illustrated this balance by oscillatory waves of prevalence of endemic diseases (Burnet 1940, p. 188). So understood, the idea of equilibrium is not inconsistent with the self/nonself model. The immune balance and self/nonself discrimination are assumed to operate at two distinct levels of biological world organization: the immune balance organizes interactions between *populations* while the self/nonself discrimination operates at the interface of an *individual* and its microbial environment. Thus there was no contradiction in Burnet's claiming that individuals face binary decision: ''eat or be eaten'' while populations are driven towards harmonious equilibrium with their parasites (Burnet and White 1972, p. 28).

Having in mind that the Burnetian notion of balance was intended to describe relationship between populations while the concept of self/nonself recognition was meant to be applicable to individuals, there is no surprise that Burnet never abandoned his balance view of the populations despite making a decisive shift towards immunology in 1957 (Sexton 1991, p. 134). As we have mentioned, he maintained and refined

this ecological outlook in the successive editions of his co-authored book *Natural history of infectious disease* (cf. Burnet and White 1972). He also used it to elucidate relationships between populations of antibody producing cells (Burnet 1959). Again, not only there is no contradiction between Burnetian self/nonself and the idea of equilibrium but the two ideas well complement each other in the Australian researcher's systems of thought.

The second domain in which immune balance was believed to operate was *the ecology of cellular and molecular interactions within the individual* (Orosz 2001; Lappe 1997). So understood, an immune balance was associated with a state of the immune system in which the suppressive and stimulatory immune reactions are equal. As a consequence, no net change is made within the system. For example, no immune response is elicited. As we have seen, this interpretation of immune balance was implicit in the work of Ehrlich and was extensively elaborated by Jerne. In fact, it is still present in various forms in immunology (for example, as equilibrium between regulatory T-cells and effector T-cells). This understanding of immune balance, like the one applicable to populations is also compatible with the self/nonself discrimination model. Self/nonself discrimination is assumed to occur at the interface of the immune system and its environment, while the immune balance in the sense elaborated by Jerne and Weigert was considered to operate *within the immune system of an individual*.

The third domain believed to be organized by immune balance was *the ecology of an individual*[1] (cf. Tauber 2008). In this sense, immune balance is a state in which the immune system of an *individual* opposes effects of environmental fluctuations that could compromise the individual's integrity. From this point of view, the function of the immune system is to tailor responses to environmental changes so that potentially damaging effects of these changes are neutralized. To play this equilibrating role, the immune system has to maintain its active state continuously. As we have seen, Metchnikoff assumed that persistence of self-tissues and foreign bodies depends on their power to counteract destructive action of phagocytes that remain continuously active. Thus, Metchnikoff could be considered as implicitly embracing the idea of

[1] This interpretation deserves special attention because, in contrast to the other two, it has direct implications for immunology. According to Burnet, immunology "is concerned with the response of the individual to invasion by microorganisms" while epidemiology deals with population-level phenomena (Burnet 1940, p. 24). From this point of view, the ecological studies developed by Burnet should be considered primarly as helping to establish "a complex, biologically informed epidemiology" (Anderson 2004, p. 39).

immune balance in this third sense. However, this concept was more explicitly elaborated by Smith and Zinsser who emphasized that parasites and hosts actively modulate their activity to counteract each other's oppressive forces. These authors maintained that it is not only the microbe but also an individual host that can fine-tune its responses to the other organism: "We have in parasitism two living variable organisms capable of adjusting themselves toward each other in a remarkable degree" (Smith 1921, p. 100). Thus, Smith and Zinsser differed from Burnet and d'Herelle in their understanding of equilibrium. Again, Burnet and d'Herelle considered equilibrium at the population level defining it as a stable ratio between parasites and hosts (d'Herelle 1926, pp. 211–212; Burnet 1940, p. 8). Instead, Smith and Zinsser considered equilibrium also at the individual level defining it as a "condition of both host and parasite which permits latter to enter the body, multiply enough and escape" (Smith 1921, p. 102).

The idea that the immune system can maintain balance in this third sense cannot be reconciled with the self/nonself model. Self/nonself model was based on the assumption that the role of the immune system is to kill foreign agents and sterilize the host. Instead, the balance view suggests that as there is no direct benefit for the microbes from killing their hosts, thus there is also no advantage for the host from killing microbes. More essential from the point of view of survival of the individual, is tailoring responses that neutralize potentially damaging fluctuations in the environment. The counterbalancing action, to be sure, may sometimes require killing. This does not mean however that killing is the immune system's principle of action. By limiting its activity to counteracting fluctuations, the immune system opens up the potential for microbes to coexist peacefully with the host.[2] If taken seriously, the balance view challenges our fundamental understanding of the immune system. Smith wrote in the context of cattle fever that "If we turn to internal phenomena, those revealed by the microscope and the numerical estimation of blood corpuscles, the line between immunity and susceptibility is somewhat less sharply drawn" (Smith 1893, p. 128). Consequently, "the boundary between normal and abnormal states is vague and shifting, and no one can tell where one begins and the other ends (Smith 1903).

Nowadays, in the face of the self/nonself paradigm crisis, the balance view is gaining an increasing attention in immunology. It is becoming

[2] It should be clear that the immune system cannot rely on isolated molecular patterns or molecular "danger signals" to tailor responses. Instead, the system has to integrate and differentiate between multiple signals to compute its states (Cohen 2007).

clear that the immune system cannot be crammed into the corset of binary logic: self/nonself, safe/dangerous, activation/inactivation. Instead, there is a continuum of states that the immune system can take to establish equilibrium with the microbes (Eberl 2010). According to Tauber, "This move from a simple on or off switch heralds a decisive shift in immunology's theoretical foundations"(Tauber 2008, p. 234). As a result, the vocabulary of immunological debates is changing, as researchers are increasingly analyzing the relationship between an individual and its microbial environment "in the language of ecological balance and disruption" (Podolsky 2012, p. 1810). The idea of infection is also being modified as it appears to result from an imbalance between the microbes and the host rather than from intrinsic pathogenicity of the former (Garrett et al. 2010; Virgin et al. 2009; Sansonetti and Di Santo 2007; Willing et al. 2011).

Current Applications of the Idea of Immune Balance: Case Study

To understand how the balance view fits into the new experimental data and replaces the traditional self/nonself paradigm, consider intestinal immune regulation. Our case study concerns the gut immune system because the intestinal epithelium covering approximately 200 m^2 is the largest surface area of a human organism that comes in contact with microbes (Gallo and Hooper 2012).

The mucosal immune system is engaged in establishing harmonious interactions with the gut environment at several different levels. At one level, the intestinal epithelial cells (IECs) modulate the continuity of the epithelial surface in response to chemical signals. Some intestinal microbes, dietary materials and other chemicals can weaken integrity of the epithelium by modifying expression and localization of intercellular tight junctions (TJs) (Ulluwishewa et al. 2011). One example includes gliadin that is a constituent of wheat which can lead to TJ rearrangement. It has been found that there is a homology between this glycoprotein and a toxin released by *Vibrio cholera* that modifies TJ proteins to invade the host (Wang et al. 2000). In response to the presence of certain bacterial ligands, immune receptors expressed on the apical surface of IECs like TLR2 can reinforce the epithelial TJs thereby counteracting their potential reconfiguration (Cario et al. 2004). Epithelial damage can also be prevented by an increase in the epithelial renewal in the presence of agents that can disrupt epithelial continuity. Certain microbial signals induce production of factors like IL-33, IL-25

or TSLP by IECs, which can in turn stimulate innate lymphoid cells in the subepithelial tissues to release IL-13, a cytokine that drives the turnover of the epithelium (Cliffe et al. 2005; Mannon and Reinisch 2012). Moreover, γδ intraepithelial lymphocytes (IEL) have been shown to release epithelial cell growth factor thereby playing an important role in tissue repair following dextran sodium sulfate (DSS) administration (Chen et al. 2002). Hence, the continuity of the epithelial surface is constantly modulated to counteract microbial and chemical changes in the intestinal lumen.

Reinforcement of the epithelial barrier is not sufficient to oppose damaging action of intestinal microbes. Their disease-causing potential is also neutralized by antimicrobial peptides (AMPs) that are released into the lumen in a controlled fashion. Specialized IECs located in small intestinal crypts, called Paneth cells, play an important role in this process. They release AMPs like defensins, cathelicidins or RegIII-γ in a strictly inducible fashion depending on the type of microbial patterns they sense though their apical PRRs (Vaishnava et al. 2008). This permits the adjustment of the repertoire of secreted AMPs to particular conditions, so that the potential of specific microbes to penetrate host tissues is limited. Specific microbes have also been shown to modulate release of AMPs by γδ IELs that sense microbial signals indirectly by receiving information from adjacent IECs (Ismail et al. 2011). The release of IgAs, the class of antibodies that can neutralize microbes restraining their power to penetrate the tissues is also dependent on specific microbial changes (Peterson et al. 2007). Stimulation of IECs by MAMPs can modulate release of factors like B cell activating factor (BAFF), transforming growth factor-β (TGF-β) or a proliferation inducing ligand (APRIL) that can condition B-cells to perform IgA class switch recombination (Cerutti and Rescigno 2008).

Apart from the release of antimicrobial molecules in response to specific microbial signals, mucus production has also been found to depend on the recognition of MAMPs as certain bacterial species, like *P. aruginosa* upregulate the release of mucin proteins by activating TLR-dependent pathways in goblet cells (Li et al. 1998). Other bacteria can induce production of mucus through TLR-independent cascades (Lemjabbar and Basbaum 2002). The importance of mucus in counterbalancing microbial proliferation and invasiveness is illustrated by the fact that deficiency of a mucin protein, MUC1 leads to an increase in the load of certain bacterial species while $Muc2^{-/-}$ mice are known to

develop spontaneous colitis (Ashida et al. 2011). Overall, the repertoire of antimicrobial molecules and mucins in the intestinal lumen is constantly modulated according to specific microbial, chemical and self-induced changes in the gut. Unique mixture of secreted molecules acts collectively to promote adaptation of an organism without engaging in ruthless killing and competition.

The activities of the innate immune cells located in the subepithelial tissues make up yet another level modulating ''tension'' between gut microbes and the host. Behavior of innate immune cells like APCs in lamina propria is strictly dependent on changes in the microbial and chemical environment in the lumen. Indirect microbial signals come to these cells from IECs that release a variety of factors depending on the type of their PRR stimulation (Rescigno et al. 2008). For example, activation of certain TLRs by microbial products induces IECs to release cytokines like TSLP, IL-12 or IL-25 that can prevent dendritic cells (DCs) from promoting differentiation of naïve T-cells into effector Th1 cells and instead may favor their development towards Th2 or regulatory T-cell phenotype (Rimoldi et al. 2005; Iliev et al. 2009a, b). On the other hand, stimulation of other apical PRRs of IECs may induce their production of proinflammatory mediators like the chemokine IL-8 (CXCL8) (Abreu 2010). Microbiota does not only control function of DCs but also their number and distribution in the tissues (Fujiwara et al. 2008; Haversona et al. 2007). Thereby, the milieu of secreted cytokines and differentiated immune cells in the connective intestinal tissues is modulated according to the changes in the microbial and chemical environment in the gut.

Microbes can also influence the activity of innate immune cells by interacting directly with their receptors. Specialized phagocytes constantly sample intestinal lumen by means of their dendritic processes (Rescigno et al. 2001). Cells located in lamina propria, like macrophages and CD103+ DCs can encounter microbes that found their way to the tissues. This however, does not necessarily entail active responses as certain microbial signals can down-regulate the activity of immune cells. For example, intestinal macrophages have been found to be hyporesponsive to TLR-stimulation (Hirotani et al. 2005) and prolonged stimulation of intestinal macrophages by a constituent of gram negative bacteria, LPS, renders them insensitive to microbial threats (Ueda et al. 2010). This indicates that presence of a microbial signal in connective tissues does not always indicate danger. This may be considered as an adaption to the presence of non-opportunistic strains of symbiotic

microbes that can find themselves in the subepithelial tissues incidentally, for example as a consequence of tissue damage. Indeed, recent evidence shows that innate immune responses are not elicited by single molecular signals. Instead, they depend on multiple signals that are integrated to produce tailored reactions (Swiatczak and Rescigno 2012). From this perspective, inflammation emerges as a physiological process whose tone is constantly regulated by interactions between multiple cellular and molecular components (cf. Cohen 2000b; Garrett et al. 2010, p. 863).

Adaptive immune responses in the gut make up still another level of reciprocal regulation between microbes and their hosts. Current evidence indicates that intestinal adaptive responses are not elicited from dormancy. Instead the adaptive immunity shifts from one active state to another to counteract changes in the microbial environment. This can be illustrated by the fact that the immune system never stops inducing differentiation of effector T-cells adjusting their repertoire to changing microbial signals. For the sake of simplicity, it is often distinguished between Th1, Th2, and Th17 responses depending on the class of differentiated T-cells that dominate an immune reaction (Weaver et al. 2007). However, as a matter of fact, immune reactions involve mixtures of various types of effector T-cells and engage a variety of non-standard types of T-cells that do not fit into the Th1/Th2/Th17 divide (cf. Matzinger and Kamala 2011). Immune responses escape categorization because each response is unique, involving a particular combination of effector and regulatory T-cells embedded into a network of immune and non-immune cells like stromal cells, epithelial cells and nerve cells that exchange signals with components of the immune system thereby reciprocally modulating their behavior and determining further steps of the immune reaction (Cohen 2000a).

All in all, intestinal immune responses are uniquely tailored to particular conditions in the gut. They depend on the composition of the gut microbes, the state of the host itself, the state of the immune system and many other factors (Swiatczak et al. 2011). On the basis of these multiple factors, the immune system creates a unique milieu of antimicrobial molecules, cytokines, chemokines and immune cells that collectively counterbalance particular environmental changes. Hence, recent studies confirm experimentally that the immune system's function is not to recognize and kill foreign agents (Cohen 2000b). Instead, the system is engaged in the permit modulation of the number and invasiveness of microbes. This mode of microbial control, despite being more complex than simple killing is more advantageous because it opens up the potential for symbiotic coexistence with microbes.

Concluding Remarks

Recent developments in metagenomics and mucosal immunology help to understand that symbiosis is not an exception but a rule and that the immune system plays as an important role in fighting pathogens as it does in establishing mutually beneficial interactions with microbes (Gilbert et al. 2012). The classical model was based on the assumption that after the self/nonself divide is settled in the embryo or in the adult, the immune system can effectively sterilize the host by eliminating agents that are recognized as foreign. Thus, this model was not able to account for the large repertoire of symbiotic associations observable in nature. It was also not in the position to explain variable responses of the immune system to agents of the same structural type. The balance view of the immune system is far better suited to accommodate these new experimental data. Instead of assuming that the immune system chases nonself strangers, it presupposes that the role of the system is to prevent damage to the host.

According to some philosophers of science, the discussion concerning the immune system function may have profound consequences for our understanding of what an organism and biological individual are (Pradeu 2012). This important problem deserves separate study. Suffices to note here that the idea of immune balance, depending on the sense in which it is used may have different implications to our understanding of an organism. Clearly, the idea that the immune system maintains balance between an individual organism and its environment is based on the assumption that the identity of the organism is predefined by genes and is not dependent on the immune system action. If the immune system opposes effects of microbial, chemical and self-induced alterations to *ensure integrity of the organism*, the identity of the organism must be already established and cannot be constructed by the very counterbalancing act. A system cannot protect, defend or ensure integrity of something that has yet not been defined. Thus, the idea of immune balance seems to be based on the same notion of living body as the one that can be found in the statement by Gilbert et al. that ''Immunity does not merely guard the body against hostile organisms in the environment; it also mediates the body's participation in a community of ''others'' that contribute to its welfare'' (Gilbert et al. 2012, p. 333). One should note, however, that the greatest value of the balance view lies not in its implicated definition of an organism, but in the fact that it helps to understand how a genetically defined individual can

become part of an anatomical, developmental, physiological, genetic, immune and evolutionary holobiont (cf. Gilbert et al. 2012).

Acknowledgments

I am grateful to William Summers from Yale for his precious comments on earlier draft of this paper and to participants of the Philosophy and Theory in Biology Young Investigators Symposium organized by Massimo Pigliucci at CUNY for helpful discussion. This paper has also benefited from extensive comments and criticisms provided by two anonymous reviewers.

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