## 1 Introduction

Human survival depends on the immune system. The traditional view of immunity is that it is designed to defend human organisms against infectious agents.[1] But its functions include more than defense. Many bacteria, viruses, fungi, and other microbes are not eliminated from the body but tolerated by the immune system and coexist with it in a symbiotic relationship.[2] Immune cells also have a critical role in cell development, tissue repair, wound healing, and elimination of debris from naturally programmed cell death.[3] The immune system does not function independently of the central nervous and other bodily systems but interacts with them in salutary or deleterious ways. Distinguishing between what is internal to the immune system and what is external to it does not explain why some immune mechanisms protect organisms or why others threaten them. Innate and adaptive immunity have evolved not only to protect us from external threats but also to maintain equilibrium within the organism.[4] The immune system's properties of defense, development, tolerance, control, maintenance, repair, and elimination enable us to adapt to and survive in the world we share with microbes.[5]

There are limitations to the immune system's natural ability to protect us from pathogens and maintain homeostasis. This is the organism's ability to regulate its internal milieu and preserve functional equilibrium. The Black Death of 1346–50 caused by the bacterium *Yersinia pestis* reduced the population in Europe, the Middle East, and Northern Africa by 30–50 percent.[6] This was the same bacterium responsible for the earlier Plague of Justinian around CE 541. Improvements in hygiene, infrastructure, and our understanding of our relationship to the environment have prevented similar bacterial pandemics. Yet morbidity and mortality from viruses and cancer underscore the limitations of immunity's protective function. Antibiotics, vaccines, and antiviral and antifungal drugs activate immune mechanisms to prevent or neutralize microbial threats to us.

But some of these threats may evade these interventions and harm us by causing disability and death. Cancer cells may disable innate and adaptive cells and proteins necessary for homeostasis and eventually lead to these same harmful outcomes. In some circumstances, components of the immune system itself, rather than pathogens, cause it to become dysfunctional. Autoreactive antibodies directed against self-antigens have been implicated in the pathogenesis of autoimmune diseases that destroy healthy cells, tissues, and organs. Proliferation of pro-inflammatory cells and proteins in response to viral infections can induce excess inflammation resulting in multi-organ failure and contribute to neurodevelopmental and neurodegenerative disorders.

It may be possible to overcome some of these limitations. Gene editing could make us and future generations less susceptible to viruses. Immune-based therapies using monoclonal antibodies can activate T cells to neutralize and destroy cancer cells. Tolerogenic drugs could prevent some components of the immune system from attacking others and reduce the incidence of autoimmune disease. They could also modulate inflammatory mechanisms in the brain and thereby prevent or mitigate the effects of neuropsychiatric disorders. These same drugs could prevent rejection of allografts transplanted from one human to another and xenografts transplanted from animals to humans.

These and other actual and possible interventions in the immune system raise ethical questions. They include: In what sense can immune functions be enhanced, and how would enhancing them benefit us? Is there a moral obligation for adults to be vaccinated against certain viruses, and to have their children vaccinated? Could refusing vaccination justifiably limit one's access to medical care? Do the therapeutic effects of immunotherapy for cancer always outweigh the actual and potentially harmful effects? Would the use of gene editing to induce immune tolerance of transplanted tissues and organs compromise protective immunity and make transplant recipients susceptible to opportunistic infections? Should researchers open the blood-brain barrier to infuse drugs into the brain to prevent or control neurodevelopmental and neurodegenerative diseases? Could this be done without altering normal neuronal processes? Should we edit genes at the germline to prevent future people from being infected by viruses or other pathogens ? Would it be bad if humans lost in competition with pathogens for survival and became extinct? All these questions regard different aspects in which humans can benefit from or be harmed by natural defects or limitations in the immune system and by attempts to intervene, or failing to intervene, in it. How one responds to these ethical questions must be informed by the cellular and molecular mechanisms of innate and adaptive immunity. This Element is an analysis and discussion of these questions.

Many philosophers use "ethics" and "morality" interchangeably in making normative judgments about actions and policies. I follow that practice here in assessing how immune function and dysfunction, and interventions to alter it, can affect persons in positive and negative ways. Although there are differences in the original meaning of these terms, they are not normatively significant. Ethics and morality both consider the rights, needs, and interests of individuals and groups, how they make claims on others, whether or how others meet these claims, and how actions and consequences that realize or defeat these claims can benefit or harm them. One benefits when an action realizes an interest one has in a certain state of affairs. One is harmed when an action defeats this interest. An action benefits a person when it makes them better off in some

respect and harms them when it makes them worse off.[7] Explicitly or implicitly, I use deontological, consequentialist, nonconsequentialist, and contractualist theories to assess normative claims about different interventions in the immune system. Deontological theories focus on actions that prioritize rights, autonomy, and duties over consequences.[8] Consequentialist theories focus on actions that bring about the best consequences.[9] Nonconsequentialist theories do not deny the normative significance of good outcomes but hold that there is no moral obligation to maximize them.[10] Contractualist theories focus on principles of action based on mutual interest and respect that no one could reasonably reject.[11]

In Section 2, I describe the main components of the immune system to establish an empirical framework within which to discuss the ethical implications of interventions to change it. I analyze and discuss whether or to what extent the immune system can be enhanced in Section 3. The most plausible conception of immune enhancement is not one of increasing circulating levels of immune cells and proteins but one that generates and maintains them at optimal levels to eliminate life-threatening antigens while tolerating non-life-threatening antigens. An enhanced immune system is one in which immunogenicity is balanced with immune tolerance. There is an equilibrium between activating and inhibitory immune cells and molecules. Interventions intended to improve or maintain immune function must ensure this equilibrium. Vaccines designed to activate B and T cells and antibodies against pathogens, as well as immunotherapy for cancer, are examples of immunogenic mechanisms. Drugs designed to prevent the production of autoreactive lymphocytes implicated in autoimmune diseases, as well as to prevent hyperacute rejection of transplanted organs from humans or nonhuman animals, are examples of tolerogenic mechanisms.

In Section 4, I discuss ethical issues surrounding vaccines. I consider some of the promises and pitfalls of developing and using vaccines to prevent or treat addictions. These issues must be framed by the social context in which addiction occurs and the view that addiction is to some extent learned behavior. I also consider questions about the justification of challenge trials involving healthy human subjects to test the safety and efficacy of vaccines for viruses such as SARS-CoV-2 (COVID-19). In discussing vaccines to prevent infectious diseases, I argue that there is a general moral obligation for widespread vaccination against the measles virus. But there may not be a similar obligation for other viruses, and I describe some circumstances in which vaccination exemptions would be permissible. I also consider whether refusal to be vaccinated justifies restricting or denying access to certain types of medical care.

In Section 5, I discuss immunotherapy for cancer. While this type of therapy can stimulate production of T lymphocytes to attack cancer cells resistant to chemotherapy, in some cases they may trigger a hyperactive inflammatory response that could damage healthy cells, tissues, and organs. The efficacy of immunotherapy in killing cancer cells would not rule out a similar type of collateral damage resulting from chemotherapy. Immunotherapy may only be offered for a limited period of time, which can influence an assessment of its benefits. Moreover, this therapy may be a treatment of last resort when all other treatments have failed. This could influence a patient's emotional state and assessment of its benefits and risks. It may also raise questions about their capacity to give informed consent to undergo therapy.

I explore possible interventions in the brain to modulate neuroimmune interactions in Section 6. Microglia and cytokines are the critical immune components in these interactions. These interventions include neuromodulating agents that might prevent or reverse excess inflammatory and other pathogenic processes in the brain. These agents would have to target neuroimmune dysregulation with a high level of specificity and at the right stage of neurodevelopmental or neurodegenerative pathophysiology to modulate dysregulated neural functions while leaving normal neural functions intact. Among the ethical issues these interventions raise is whether it would be permissible to enroll individuals deemed at risk of developing a neurological or psychiatric disorder but who are asymptomatic in research to test their safety and efficacy.

In Section 7, I discuss the use of genetic engineering of the immune system to overcome allograft and xenograft rejection in tissue and organ transplantation. By targeting the genetic mechanisms at the source of graft rejection, gene editing may be more effective in promoting successful human-to-human and animal-to-human transplantation than tolerogenic drugs modulating natural molecular mechanisms. But it cannot be assumed that altering the immune system's recognition of foreign antigens from tissue would leave all other immune functions intact. I consider the possibility of germline gene editing to eliminate susceptibility to viruses. This requires discussion of the unknown possible long-term benefits and risks of using this technique in people who exist now and those who will exist in the future. I also consider somatic cell gene editing of immunity to treat certain diseases. While this technique does not entail the risk of transmitting unwanted adverse effects to offspring, as in germline editing, it may still entail some risk. In the final Section 8, I speculate on the possibility that humans and their immune systems could one day lose in the competition with life-threatening microbes and consider whether this would be good, bad, or morally neutral.

## 2 The Human Immune System

The immune system is a complex set of functions that normally overlap and interact in a coordinated way to maintain homeostasis within the organism and protect it from pathogens (Figure 1).[12] The evolutionarily older innate system is activated and responds generally and nonspecifically to microbes perceived as threats to destroy and clear them from the organism. The main components of the innate immune system are dendritic cells, macrophages, neutrophils, eosinophils, phagocytes, natural killer (NK) cells, and complement. This last component is a set of proteins that mediate immune functions such as inflammation, cell lysis (when the cell membrane ruptures and dies), and tagging microbes for phagocytosis (the engulfment of microbes for elimination). As the name implies, these proteins complement the action of other immune cells and molecules. This is one respect in which innate and adaptive systems interact. The function of phagocytes to present antigens to T and B lymphocytes is another.

The evolutionarily more recent adaptive immune system consists mainly of B and T cells (B and T lymphocytes) in the tissue between the body's cells, and antibodies in the blood and other bodily fluids. T cells are produced by the thymus gland, and B cells are produced in the bone marrow. Once they reach full maturity, these cells migrate to and reside in the lymph nodes and spleen. T cells are one type of cell that produces cytokines. These signaling protein molecules regulate immune cellular communication. Cytokines also mediate inflammatory responses to infectious agents. They include chemokines, interleukins, and interferons. Cells in both innate and adaptive immune systems produce cytokines.

Adaptive immunity is divided into humoral and cell-mediated types. Humoral immunity (from the idea of bodily "humors") consists of antibodies,

| Innate immune system | Adaptive immune system |
|---|---|
| Dendritic cells | T cells (T lymphocytes, e.g., CD4+, CD8+) |
| Macrophages | B cells (B lymphocytes) |
| Neutrophils | Antibodies: antigen-specific, produced by B cells |
| Eosinophils | Cytokines released by adaptive immune cells, especially helper T cells |
| Phagocytes | |
| Natural killer (NK) cells | |
| Complement | |
| Cytokines (chemokines, interferons, interleukins) released by innate immune cells | |

**Figure 1** The human immune system: main components

which are immunoglobin molecules activated in response to an antigen. B cells contribute to humoral immunity by producing antibodies. There are five types of immunoglobins: IgG, IgM, IgA, IgD, and IgE. They circulate in the blood and on cell surfaces. An antigen is any biological entity that combines with antibodies and triggers their response to it. Antigens may be from sources external or internal to the body. They may be present on microbes such as bacteria, viruses, fungi, tissue in transplanted organs, and cancer cells. An antigenic epitope is the smallest identifiable part of an antigen with which an antibody specifically interacts. "In general, the more complex the antigen, the more stimulatory or immunogenic it will be in eliciting an immune response."[13] As I explain in the next section, "immunogenic" may refer to both positive and negative effects in the organism and beneficial and harmful effects in persons. This depends on the type and level of immune response that an epitope elicits.

Cell-mediated immunity consists mainly of mature T cells. They interact with cytokines released in response to an antigen, as well as with macrophages and phagocytes. T cells do not produce antibodies but regulate B cell responses to antigens. Effector B and T cells activate a range of immune functions. Cell-mediated immunity does not rely on antibodies. CD4+ and CD8+ cells are two types of T lymphocytes in antigen-specific activation. The first type, also called "helper T cells," produce cytokines. The second type, also called "cytotoxic T cells," produce cytokines as well and initiate a process resulting in cell death. Effector B and T lymphocytes stimulate the production of other immune cells. In addition to mediating B cell functions, regulatory T lymphocytes down-regulate overactive immune processes and thereby promote immune tolerance of certain foreign and self-antigens. Another key factor in immunity is the major histocompatibility complex (MHC). This is a collection of genes controlling different immune functions. The MHC regulates T cell responses to foreign tissue antigens as well as T cell autorecognition. Human leukocyte antigen (HLA) is the human version of MHC. HLA has a critical role in immune surveillance and the immune response to transplanted solid organs and tissues.

The hallmark of the adaptive system is immunological memory. B and T cells that have encountered an antigen can respond more effectively in subsequent encounters with it than innate immune cells and proteins. For this reason, they are described as memory B and T cells. In contrast to the generalized, nonspecific rapid response of the innate system to an infectious agent, the more specific response of the adaptive system may take days or even weeks to occur as it forms a memory of the antigen following an initial encounter with it. Like antibodies, B and T lymphocytes are antigen-specific. This enables an adaptive response that targets a particular perceived threat to the organism.

The success or failure of an adaptive response to a pathogen depends on whether, or to what extent, antibodies and memory B and T cells recognize the antigen it expresses after an initial exposure. The ability of immunological memory to protect us from pathogens may be limited by the fact that most antigens contain a variety of epitopes, and activation of antibodies and effector T cells may vary depending on different receptors for different antigen epitopes. How antibodies and cells respond may be influenced by *antigenic drift* and *antigenic shift*.[14] The first refers to the process in which there is an accumulation of genetic errors during viral replication. The second refers to the process in which recombination causes changes in the dominant antigen expressed by a virus. These processes influence *antigenic variation,* the mechanism by which a protozoan, bacterium, or virus evolves by altering the proteins on its surface to avoid a host immune response. This can impair the ability of vaccines to control them because they cannot target a specific antigen. It may promote *antigenic sin*.[15] This refers to the immune system's tendency to preferentially respond to an antigen from a previous infection when a second slightly different version of the antigen is encountered. The response depends on the organism's immune history.

Antigenic sin is one hypothesis for the high mortality rate among young adults during the 1918 influenza pandemic. They were probably exposed to the H3N8 influenza strain when they were born around 1889–1890. This exposure may have "primed" their immune systems to respond to the antigen from this virus instead of to the antigen (epitope) from the H1N1 virus of 1918. The "sin" was the immune system's failure to recognize and respond to the more immediate and virulent pathogenic threat. In proposing this hypothesis, Alain Gagnon and coauthors explain that "developing immunological memory to an antigenically dissimilar subtype in early life may actually subvert the immune system, thereby increasing the risk of death when the individual is infected by a novel strain later in life."[16] The older memory was the predominant memory controlling the response to the H1N1 epitope. Older adults did not have the same rate of mortality as younger adults probably because of immunologic cross-protection from earlier exposure to the virus that was circulating in the population before the 1889–1890 influenza pandemic. "One mechanistic explanation for this is that conserved, but non-neutralizing epitopes, on the secondary viruses elicit a memory antibody response generated during the first infection that is faster and greater in magnitude than the *de novo* response, but not protective against the new strain. As a result, these memory cells essentially out-compete the protective cells that would normally be newly generated against the subsequent exposures."[17]

Innate and adaptive immunity interact in many ways. Complement in the innate system interacts with cytokines in the adaptive systems in mediating

inflammation. Macrophages in the innate system activate and interact with B and T lymphocytes that target antigens. The memory of the antigen in these lymphocytes induces a more vigorous response to it. Lymphocytes also recruit other cells and soluble proteins to remove microbes from the body. In addition, cytokines continue inflammatory processes initiated by macrophages and complement to destroy pathogens. These interactions may complicate interventions designed to improve specific immune functions. Altering some functions may also alter others in ways that may not always be salutary or benign.

The idea that the immune system has evolved to protect the organism from microbial threats previously led some researchers to draw a "self-nonself" distinction in immunology.[18] Endogenous cells and proteins (self) protect the organism; exogenous agents (nonself) threaten it. But more recent research has shown that whether these molecules are internal or external to the organism does not determine whether they promote health or disease. Rather, what determines this is whether they maintain or disrupt homeostasis.

Foreign antigens on bacteria, fungi, and other microbes may be tolerated rather than rejected to preserve functional equilibrium. The body's own immune cells can disrupt it in different forms of pathological autoreactivity. This may occur from molecular mimicry.[19] When the immune system encounters an infectious agent, there may be a cross-reactive immune response to a self-antigen that is molecularly similar to a foreign antigen expressed by a pathogen. This similarity can cause T cells to mistake one antigen for the other and direct antibodies to attack and destroy the infected individual's own healthy cells. This is one explanation for the pathogenesis of autoimmune diseases such as type 1 diabetes, where autoreactive lymphocytes and autoantibodies attack and destroy pancreatic islet cells that produce insulin. There is cross-reactivity between B and T cells and molecular fragments of the coxsackie virus and cytomegalovirus, which can cause these cells and antibodies to become autoreactive. Cross-reactivity and the inflammatory response it elicits might also partly explain the destruction of myelin (the sheath that insulates nerve cell axons that conduct electrical impulses in the brain) in multiple sclerosis.

Pro-inflammatory cytokines are necessary to destroy infectious agents. But chronic hypersecretion of these signaling protein molecules can damage healthy tissues and organs. These "cytokine storms," or "cytokine release syndromes," are "life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune cell hyperactivation that can be triggered by various therapies, pathogens, cancers, autoimmune conditions, and monogenic disorders."[20] They have been cited as one explanation for the high mortality rate from pulmonary inflammation and lung damage among young

adults in the 1918 influenza pandemic and older adults in the first two waves of the SARS-CoV-2 pandemic in 2020 and 2021.

Autoimmune diseases and cytokine release syndrome illustrate that the immune system's own cells and molecules do not always promote the health and survival of the organism. Pharmacological attempts to induce innate and adaptive tolerance rather than elimination of non-life-threatening viral antigens and antigens on transplanted tissue to prevent graft rejection are examples that blur the distinction between self and nonself. Passive transfer of the immunoglobin IgG across the placenta during pregnancy is an example of natural immune tolerance of foreign antigens. Another example is gut microbiota and other microbes in the body that have a symbiotic relationship with immune functions. They contribute to cell development, tissue repair, and eliminate debris from cell death in their interaction with neutrophils and macrophages.

Whether immunity is regulated or dysregulated depends on how innate and adaptive systems respond, or fail to respond, to different antigens in destroying or tolerating them. While destructive responses to life-threatening antigens seem to support a distinction between the immune self and nonself, tolerance of other antigens suggests that there is a continuum from one to the other. Destruction and tolerance are not programmed into immune functions but depend on how the immune system perceives antigens and other molecules in different biological circumstances. "Immune defense and pathogenicity are not intrinsic properties of host and microbes. Rather, they are a matter of evolutionary and ecological context."[21] In some contexts, tolerating an antigen can promote adaptability and survival of the organism. In others, eliminating the antigen is the only way to achieve these goals.

Thomas Pradeu outlines two main problems with the self-nonself theory of immunity:

> First, far from being always pathological, autoimmunity has been proved to be a necessary component of everyday immunity. A degree of autoreactivity (ie., a reaction to "self") characterizes the lymphocytes generated and selected in primary lymphoid organs as well as naive lymphocytes always circulating in the periphery . . . Effector T cells are selected only if they react weakly to self elements (and not if they do not react at all). There exists in fact a continuum from autoreactivity (interactions between immune receptors and endogenous motifs) and to autoimmunity (the triggering of an effector response targeting endogenous motifs) and to autoimmune diseases (only the latter situation is pathological . . . ) it consists in the destruction of endogenous components, in a sustained manner and on a large scale – a given organ or even the whole organism in the case of systemic autoimmune diseases such as lupus.[22]

> Second, many genetically foreign entities are not eliminated by the immune system and are instead actively tolerated via regulatory immune responses. This includes examples such as foeto-maternal tolerance and various forms of chimerism, but also, and most crucially, immunological tolerance to a large number of bacteria, archaea, viruses, and fungi at all of the body's interfaces, including the gut, skin, lungs, sexual organs, and so on . . . Immunological interactions between host and microbes enable, in general, a peaceful coexistence between these two partners.[23]

Pradeu concludes: "The upshot is that the self-nonself theory is inadequate or at least incomplete because many self components trigger immune responses and many nonself components are actively tolerated by the immune system."[24]

The identity of an organism does not exclude but includes microbes. In many circumstances, however, tolerance of and coexistence with certain microbes are not compatible with the organism's survival. Some antigens can overwhelm the immune system and lead to the organism's demise. Innate and adaptive immunity must not tolerate but eliminate them. Again, though, whether tolerance or elimination is most conducive to survival does not depend on whether a biological entity is endogenous or exogenous to the organism. Rather, it depends on whether an antigen poses a threat to the organism and how different components of the immune system respond to the antigen.

## 3 Can the Immune System Be Enhanced?

Some bioethicists have discussed the idea of enhancing immunity.[25] Typically these are general claims about how genetic manipulation could improve immune functions without much detail about how this would occur. Immunologists and scientists in related fields often use "augment," "boost," and "enhance" interchangeably. The general idea of enhancement suggests interventions in the immune system that would provide more protection against infectious agents than what it naturally provides. It also suggests interventions that would prevent it from turning against itself.

"Enhancement" has been defined by bioethicists and philosophers as any intervention "designed to improve human form or functioning beyond what is necessary to sustain or restore good health."[26] "Therapy" can be described as any intervention that restores or maintains good health. This may include preventive measures. Some argue that there is no clear distinction between enhancement and therapy. John Harris claims that "treatments or preventive measures which protect humans from things to which they are normally vulnerable, or which prevent harm . . . are necessarily also enhancements."[27] It is unclear whether any intervention designed to improve the immune system could do more than maintain homeostasis and protect the organism from microbial